DISSERTATION

on

ASSESMENT OF MEAN PLATELET VOLUME IN ISCHEMIC STROKE AND ITS CORRELATION WITH PROGNOSIS AND SEVERITY

submitted in partial fulfillment of
requirements for

MD DEGREE EXAMINATION

BRANCH-I GENERAL MEDICINE

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CERTIFICATE

This is to certify that the dissertation titled **"ASSESMENT OF MEAN PLATELET VOLUME IN ISCHEMIC STROKE AND ITS CORRELATION WITH PROGNOSIS AND SEVERITY "** is a bonafide work done by **Dr. C. POORNIMA RAJ**, Post Graduate student, Institute of Internal Medicine, Madras Medical College, Chennai – 600003, in partial fulfillment of the university rules and regulations for the award of MD DEGREE in GENERAL MEDICINE BRANCH-I, under our guidance and supervision, during the academic period from April 2010 to April 2013.

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DECLARATION

I solemnly declare that the dissertation titled **"ASSESMENT OF MEAN PLATELET VOLUME IN ISCHEMIC STROKE AND ITS CORRELATION WITH PROGNOSIS AND SEVERITY"** was done by me at Madras Medical College, Chennai – 600003, during the period May 2012 to October 2012 under the guidance and supervision of Prof. N. RAGHU, MD, to be submitted to The Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of MD DEGREE in GENERAL MEDICINE BRANCH-I.

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ABBREVIATIONS

CVA	Cerebro Vascular Accident
TIA	Transient Ischemic Attack
MI	Myocardial Infarction
APLA	Anti Phospholitid Antibody Syndrome
ATP	Adenosine Triphosphate
ADP	Adenosine Diphosphate
NOs	Nitric Oxide synthase
CNS	Central Nervous System
ACA	Anterior Cerebral Artery
PCA	Posterior Cerebral Artery
AICA	Anterior Inferior Cerebellar Artery
PICA	Posterior Inferior Cerebellar Artery.
ICA	Internal carotid artery.
mRS	Modified Rankin's Scale

DALY	Disability Adjusted Life Year
CT	Computed Tomography
MRI	Magnetic Resonance imaging
LACS	Lacunar Syndrome
fL	Femtolitre
PF4	Platelet Factor4
TGβ	Transforming Growth Factor β
MPHA	Megakaryocyte Platelet Haemostatis Axis
MK	Megakaryocyte
MPV	Mean Platelet Volume
PC	Platelet Count
PDW	Platelet Distribution Width
L-PCR	Platelet Large cell Ratio
EDTA	Ethylene Diamine Tetra Acetic Acid
vWF	Von Willebrand Factor
PROGRESS	Perindopril Protection Against Recurrent Stroke Study

CML	Chronic Myeloid Leukemia
ITP	Immune Mediated Thrombocytopenia
DM	Diabetes Mellitus
SHT	Systemic Hypertension
CAD	Coronary Artery Disease
LDL	Low density lipoprotein
HDL	High density lipoprotein

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INTRODUCTION

Stroke is the most common neurological disorder worldwide and it is the most frequent of all the neurological disorders. Stroke is also known Cerebrovascular Accident (CVA), derived from Greek word in the year 1599 which means 'Struck Down'[1]. It is the disease of developed nations.

According to the World Health Organization, 15 million people suffer from stroke worldwide every year. Of these, 5 million die and another 5 million are permanently disabled[2].

The incidence of stroke is higher in men than in women. Every year there are about approximately 700,000 cases of stroke, roughly 600,000 ischemic lesions and 100,000 hemorrhages, with 175,000 fatalities from these causes.[3]

It is estimated that by the year 2020 stroke will become the 4th leading cause of disability adjusted life years.[4] The prevalence of stroke in India is estimated to be 203/100000 population above 20 years of age. The disability and morbidity is higher in elderly with doubling of death due to stroke in United States by the year 2030.[5]

Cerebrovascular Accident is defined as the abrupt onset of focal neurological deficit. It was described as if the patient was struck by the hand of God. Stroke may be due to ischemia or hemorrhage, 87% of the stroke are ischemic. Occurrence of stroke leads to a lot of physical disability and also cognitive and behavioral impairment. The most important risk factors that contribute to stroke are Systemic hypertension, Diabetes mellitus, dyslipidemia, Cigarette smoking and heart diseases. These risk factors causing stroke when modified and kept under strict control have substantial influence in preventing its occurrence and reducing its severity.

The platelets play a major role in pathogenesis of vascular disease. Platelet size and function is measured by Mean Platelet Volume (MPV). Platelet activity is accentuated in acute ischemic stroke due to blood vessel occlusion that leads to ischemia, endothelial damage and new platelet formation. The new younger platelets are larger in size due to increase in α granules and the presence of platelet factor 4. Thus the mean platelet volume is elevated in ischemic stroke. Studies conducted worldwide, have found that mean platelet volume has prognostic significance in determining the outcome and severity of stroke. Similar studies have not been conducted much in our country. In this study the prognostic significance of Mean platelet volume has been assessed and its significance evaluated.

AIMS AND OBJECTIVES

- **PRIMARY OBJECTIVE**:

  Analyze the Mean Platelet Volume in patients who have suffered an ischemic stroke when compared to a control population.

- **SECONDARY OBJECTIVE(S)**:

  a. Analyze the association between Mean Platelet Volume and severity of ischemic stroke (which can be based on modified Rankin's scale at 1 week after ischemic stroke and on outcome at 1 month)
  b. Analyze the effect of comorbid illnesses (such as Diabetes, Hypertension, Dyslipidemia) on Mean Platelet Volume in ischemic stroke patients.
  c. Analyze the effect of drugs (such as Aspirin, Clopidogrel, Statins, ACE inhibitors, Anticoagulants[in AF with stroke]) by comparing Mean Platelet Volume values at admission and after 1 month during which period the patient may have been started on any of the above medications.

REVIEW OF LITERATURE

Stroke is the most common neurological disorder worldwide and it is the most frequent of all the neurological disorders.

About 2,400 years ago in the year400 BC the father of medicine, Hippocrates described stroke as sudden onset of paralysis and coined the term Apoplexy, a general term used by physicians which means struck down with violence[6]. As there were numerous conditions that lead to sudden paralysis, the term apoplexy did not indicate a specific diagnosis.

Followed by Hippocrates, Johann Jacob Wepfer was the one who investigated the pathological signs of apoplexy. He was the first to identify the postmortem signs of bleeding in the brains of patient who died of apoplexy. From autopsy study he gained the knowledge of carotid and vertebral arteries supplying blood to the brain. He suggested that the blockage of the main arteries can also lead to apoplexy in addition. Thus in the year 1928 apoplexy was categorized depending on the blood vessel pathology which lead to the term Stroke or Cerebrovascular disease ("cerebro" means part of the brain, vascular refers to blood vessels)[7]

In humans, the moment the blood vessel gets occluded the brain damage begins and continues for days afterwards. So there is a very short window period for the treatment of most common forms of stroke. Because of this the significance of prevention is to be highlighted and primary preventive strategies need to be identified.

PREVALANCE OF STROKE

Stroke is the disease of developed and the rich nations. The incidence of stroke is higher in men than in women. It is more common in the elderly but can occur at any age. Every year there are about approximately 700,000 cases of stroke, roughly 600,000 ischemic lesions and 100,000 hemorrhages, with 175,000 fatalities from these causes.

It is estimated that by the year 2020 stroke will become the 4th leading cause of disability adjusted life years (DALY).

Stroke is defined as a sudden occurrence of a non conclusive, focal neurological deficit, described as if the patient has been struck by the hand of God.

Stroke may be due to ischemia or hemorrhage. 87% of all stroke are ischemic.[8]

RISK FACTORS

- The most important risk factor that ranks first in association with stroke is Systemic Hypertension. It has been proved that the control of blood pressure will decrease the risk of occurrence of stroke in an individual.
- The other risk factors are
    - Diabetes.
    - Hyperlipidemia.
    - Smoking – Increase the rate of Carotid atherosclerosis
    - Atrial fibrillation – mainly due to cardiac cause.
    - Infective endocarditis (Bacterial and Non bacterial) leading on to embolic stroke.
    - Right to left shunts
    - Systemic – Hypercoagulable conditions like APLA.
    - Usage of Oral Contraceptive Pills.
    - Symptomatic Carotid Artery Stenosis-70-99% of patients develop stroke.

ISCHEMIC STROKE

Ischemic Stroke refers to occurrence of stroke due to decreased cerebral perfusion due to thrombosis or embolism.

ETIOLOGY:

The following table enlists the common and uncommon causes.

Common Causes	Uncommon Causes
Thrombosis	**Hypercoagulable disorders**
Lacunar stroke (small vessel)	Protein C deficiency
Large vessel thrombosis	Protein S deficiency
Dehydration	Antithrombin III deficiency
Embolic occlusion	Antiphospholipid syndrome
Artery-to-artery	Factor V Leiden mutationa
Carotid bifurcation	Prothrombin G20210 mutation
Aortic arch	Systemic malignancy
Arterial dissection	Sickle cell anemia
Cardioembolic	Thalassemia
Atrial fibrillation	Polycythemia vera
Mural thrombus	Systemic lupus erythematosus
Myocardial infarction	Homocysteinemia

Dilated cardiomyopathy	Thrombotic thrombocytopenic purpura
Valvular lesions	Disseminated intravascular coagulation
Mitral stenosis	Dysproteinemias
Mechanical valve	Nephrotic syndrome
Bacterial endocarditis	Inflammatory bowel disease
Paradoxical embolus	Oral contraceptives
Atrial septal defect	Venous sinus thrombosisb
Patent foramen ovale	Fibromuscular dysplasia / Vasculitis
Atrial septal aneurysm	Primary CNS vasculitis
Spontaneous echo contrast	Systemic vasculitis

Few rare causes of ischemic stroke includes:

Hypercoagulable disorders:

A variety of disorders are associated with increased risk of thrombosis. Protein C and S deficiency cause arterial thrombosis. SLE, Limbman Sacs endocarditis causes embolic stroke. Sickle cell anemia is a common cause of stroke in children.

Fibromuscular Dysplasia:

Fibromuscular Dysplasia affects the vertebral arteries commonly and is more common in women. Usually an incomplete occlusion occurs. Renal artery involvement is common and may cause hypertension. Usually asymptomatic but may be associated with audible bruit, Stroke.

Temporal (Giant Cell) Arteritis:

Temporal (Giant Cell) arteritis is common in old age. Temporal arteries undergoes gramulomatous inflammation with giant cells.

Takayasu Arteritis:

Takayasu arteritis or idiopathic giant cell arteries involves the great vessels like aortic arch, carotid or vertebral artery leading to thrombosis.

Moya Moya Disease:

Moya Moya disease involves the large arteries commonly. The occlusion occurs at the stem of Middle Cerebral Artery and Anterior Cerebral Artery. The presense of collateral circulation gives the appearance of puff of smoke.

Reversible Posterior Leukoencephalopathy:

There is an extensive cerebral segmental vasoconstriction leading to cerebral ischemia. The pathophysiology is uncertain but the ischemia is reversible completely.

Leukoaraiosis:

Leukoaraiosis or Periventricular white matter disease causes multiple small vessel infarcts within the subcortical white matter. It is due to lipohyalinolysis of small penetrating arteries. It commonly occurs in chronic SHT.

CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy) most commonly presents as small vessel stroke.

TRANSIENT ISCHEMIC ATTACK (TIA):

If the neurological sign and symptoms resolve within 1 day (24 hours), irrespective of imaging evidence of new brain changes , it's termed as Transient IschemicAttack.[10]

One third of TIA occurs in patients with hypertension. They are preceded or followed by stroke. In 20% of TIA stroke occurs within one month and in 50% within one year.[11] TIA is the warning sign of an impending blood vessel occlusion.TIA of longer duration ,multiple episodes each with different pattern is most probably due to embolism, whereas recurrent brief attacks with similar pattern are mostly due to atherosclerosis and thrombosis.

TIA can also occur due to increased viscosity of the blood, as in hypercoagulable states, polycythemia vera, Leukemia. It occurs most commonly in vertebro basilar system rather than in the carotid system.[13] The risk of occurrence of myocardial infarction is high after transient ischemic attack.

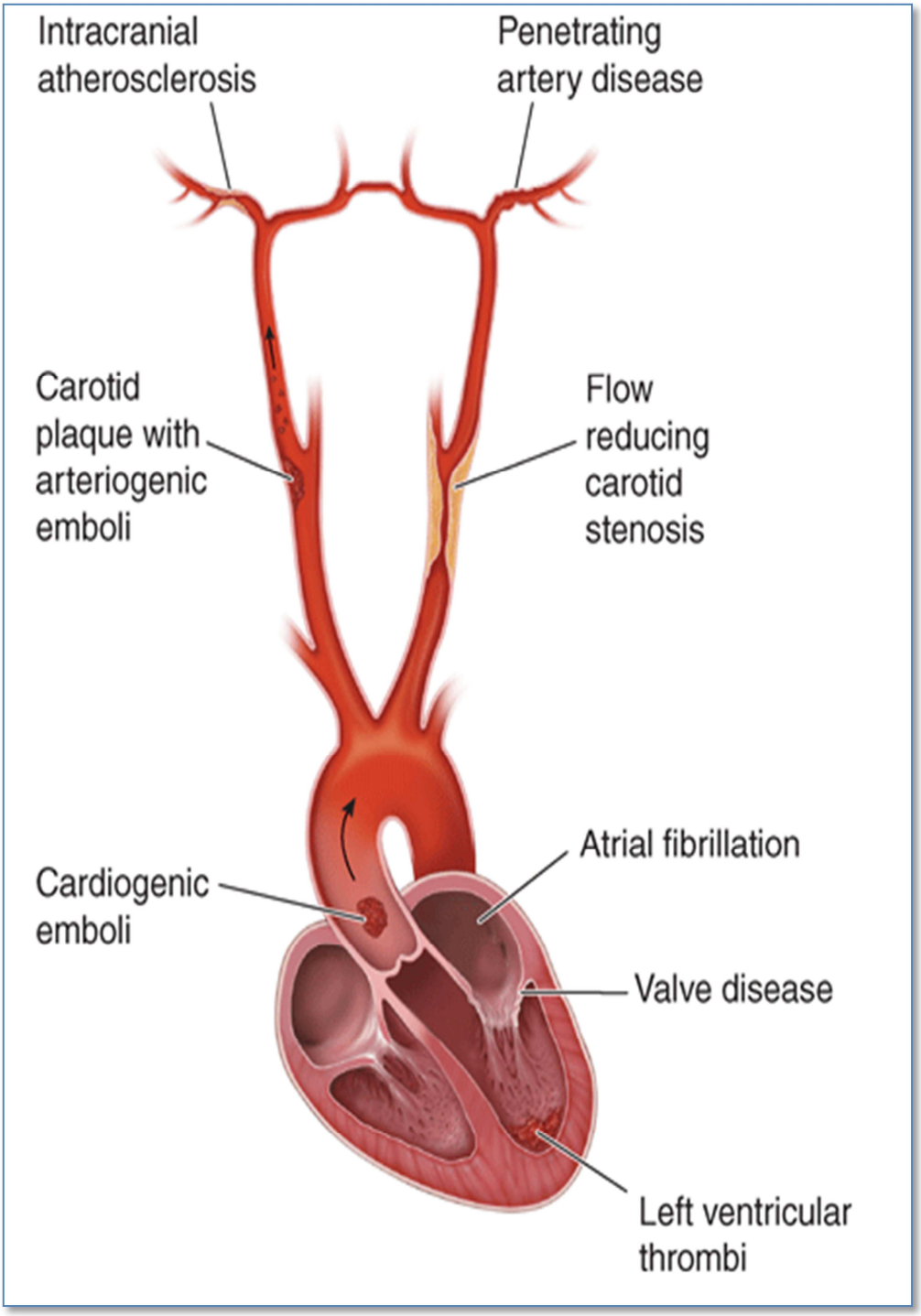
PATHOPHYSIOLOGY OF ISCHEMIC STROKE:

The pathophysiology of occurrence of ischemic stroke depends on its etiology and risk factors. The pathology may be either due to thrombus or embolism or decreased perfusion due to stenosis in arterial system causing occlusion.

- Altered permeability of vessel wall
- Change in the viscosity mainly increased viscosity of the blood
- Blood vessel rupture
- Atherosclerosis

- Aneusymal dilatation
- Hypertension
- Atheroscelerosis.
- Arteritis and vasospasm
- Developmental malfunction.

It is difficult to distinguish the lesion of an embolism or thrombosis. Embolic stroke occurs suddenly and the neurological deficit is to the maximum at the onset. Thrombotic stroke occurs less abruptly and takes longer time for the stroke to evolve. Thrombosis of vessels may lead to artery to artery embolism. The stenosis occurs most commonly due to atherosclerosis and plaque deposition.



Stenosis, Embolism and Thrombosis are shown in this diagram.

The extent of ischemia depends on degree and duration of occlusion and also the presence or absence of other associated factors like

- Blood pressure:

  Systemic blood pressure determines the cerebral perfusion pressure. When blood pressure is lowered the cerebral perfusion pressure also decreases leading to global cerebral ischemia.

- Hyperthermia:

  Ischemic injury is much severe if there is elevated body temperature.

- Glucose level:

  Both hypoglycemia and hyperglycemia are associated with a poorer outcome.

- Hypercoagulable state:

  If there is an associated hypercoagulable state there is an increase in micro thrombi formation and worseninig of blood vessel occlusion.

NEURONAL DEATH:

Neuronal death occurs by two ways:

- Apoptosis:

  Apoptosis is defined as programmed cell death that occurs in neurons in certain conditions like ischemia. The nucleus is damaged first followed by activation of suicide proteins in the nuclei, that begins the autolytic process resulting in cell death. This process is mediated by DNA cleavage. The process of apoptosis takes only 1 hour.[12]

- Coagulation Necrosis:

  Coagulation necrosis is a process by which cell death occurs without inflammation. This is due to damage to the plasma membrane by physical and chemical stimuli. The cell initially swells then shrinks. This process takes 6-12 hours to evolve. By 24 hours there is complete necrosis.[13]

  The morphology of cell death in apoptosis is different from cell death due to coagulation necrosis.[14]

- Thrombosis:

  Atherosclerosis is the most common pathological cause for the occlusion of blood vessel that leads to thrombosis.The plaque that is formed may be fractured ulcerated or calcified. Damage to the endothelium activates

vasoactive enzymes and release various factors that contribute to thrombosis and occlusion[15].

The other pathological causes of thrombosis is hypercoagulable state by formation of clot, micro thrombi that occurs in conditions like Giant cell Arteritis, APLA.

- Lacunar Infarcts:

  Lacunar Infarct is due to the occlusion of small penetrating arteries arising from the cerebral arteries . These may be 100-400 mm in diameter. The size of the infarct is about 20mm in diameter. The pathology is due to lipohyalinolysis.[16,17] The incidence is around 10-30% of all strokes. In people with chronic hypertension, the small arterioles are tortuous, long and forms microaneurysm that makes the arteriole susceptible to occlusion.

- Embolism:

  Embolisation of artery may be due to various causes and the most common cause is Cardiac source. Most of the emboli occludes the middle cerebral artery, because 80% of the the blood flow occurs through this artery.[18] Apart from this the superficial branch of cerebral and cerebellar arteries are involved though less frequently. The embolic occlusion can also cause vasospasm by acting as an irritant to the blood vessel. Vasospasm is the

more frequent in younger than the elder patients, because blood vessels in younger individuals are not much atherosclerotic.

The important determinants of pale or hemorrhagic infarct are

a. The size of the infarct
b. The adequacy of the collaterals
c. The initiation of therapy like anticoagulants and thrombolysis

Hypertension is not the independent risk factor for hemorrhagic infarct.[19,20]

- Global Ischemia:

Global Ischemia is also known as the Hypotensive stroke. Systemic hypotension due to any cause can lead to global ischemia. The most commonly affected cells are pyramidal cell layer of hippocampus and the purkinje cell layer of cerebral cortex. The grey matter in cerebrum is also susceptible to this ischemia. It occurs most frequently in the water shed area, that is present at the junction of anterior, middle and posterior cerebral arteries. 10% of the infarct are water shed infarcts. It occurs due to carotid stenosis in 40%.[21]

The clinical presentation of water shed infarct is weakness, sensory involvement involving the upper limb more than the lower limb, face is usually spared and the speech is not affected.

Unlike any other organs, Brain depends entirely on glucose for its metabolism as it lacks Glycogen which stores glucose, and brain also lacks the anaerobic metabolism. The centres in the lower brain stem regulate the constant blood supply to the brain by stimulation of Vasomotor reflexes and Baroreceptors. Decrease in blood flow for even 4 to 10 minutes produces a rapid symptom of neurological deficit.[22]

The normal cerebral blood flow is 50-60 ml/100 gm/min.[23] Below this level there is cerebral vasodilatation, the collaterals get opened and the oxygen extraction from the other cells increases. When it is less than 20ml/100gm/min, the cerebral auto regulatory mechanism gets impaired. The brain tissue goes for infarction over an hour, if the blood flow is 16-18ml/100gm/min. And finally irreversible neuronal injury occurs if blood flow is less than 10ml/100gm/min.[24]

Once the infarction had occurred there is increased water accumulation immediately both intracellularly and in intercellular spaces leading to swelling of the infarcted area. There is a release of inflammatory mediators and leucocyte gets recruited .These released mediators cause vasodilation and platelet aggregation. The immunoregulated platelets, erythrocytes and leuckocytes gets adhered to the vessel wall leading to occlusion and ischemia.

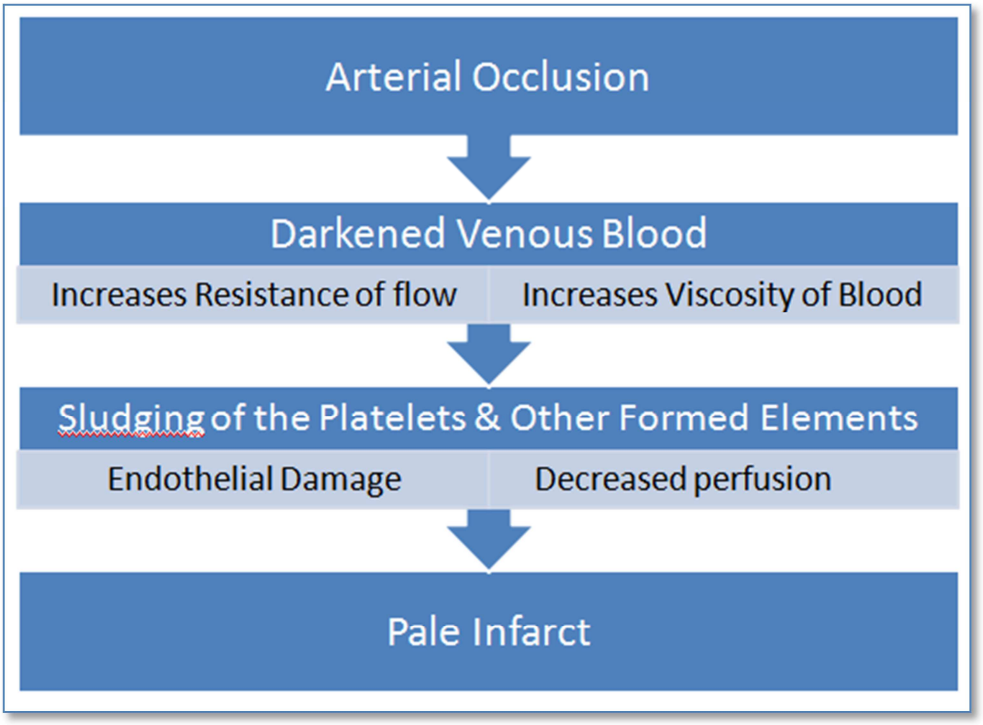
When brain tissue completely is completely deprived of the blood flow leading to irreversible neuronal destruction, it's termed as Global Ischemia. If the collaterals are able to maintain the blood flow and oxygen it is known as focal ischemia

The core region surrounding infarcted area is ischemic. This zone is known as ischemic penumbra, which has viable neurons and marginal perfusion.[25]Maintaining the blood flow to this ischemic penumbra is the targeted factor in ischemic stroke because this ischemia area recovers from injury once the flow is re-established but when the flow is not reversed it goes for infarction leading to worsening of the clinical status and outcome. Ischemic penumbra is seen in MRI / CT – perfusion- diffusion imaging. The newly emerging modalities of treatment like Revascularisation therapies are aimed at saving the ischemic penumbra to prevent further infarction.

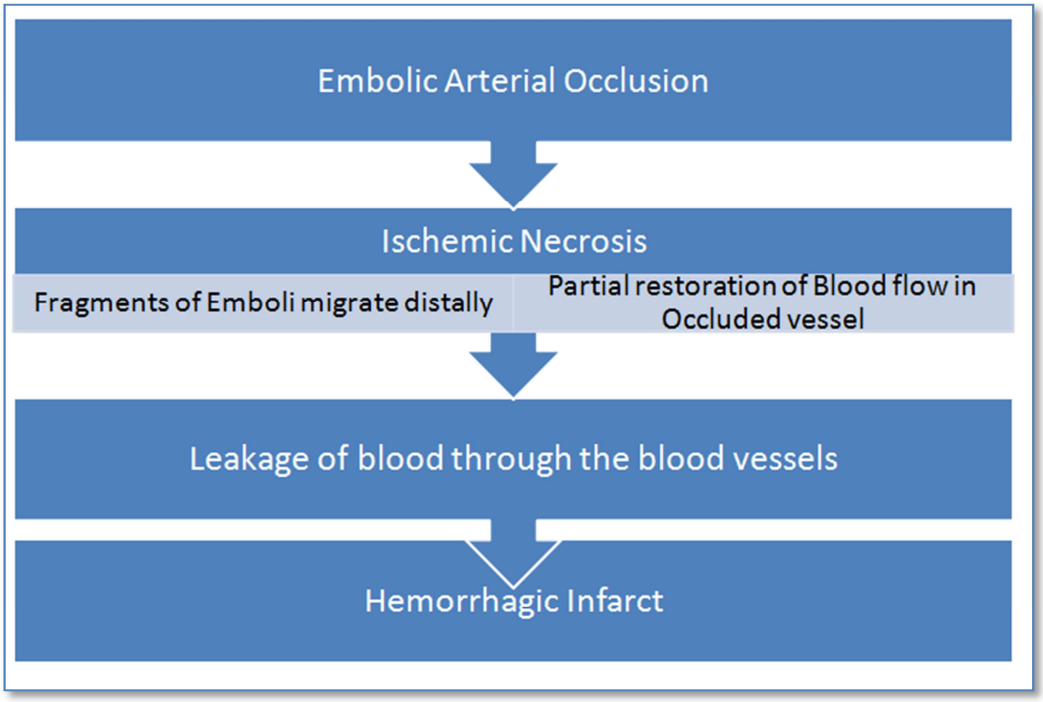
There are two types of infarct

- Pale Infarct
- Hemorrhagic Infarct

a) Pale Infarct



b) Hemorraghic Infarct



BIOCHEMICAL CHANGES:

These depolarised cells when injured produces efflux of potassium, depletion of ATP and Creatine kinase. *Groen et al* proposed that low serum potassium increases the stroke rate[26]. Accumulation of free fatty acids destroys the phospholipids in cell membranes of neurons, which alters the calcium homestasis. These changes lead to histological features of necrosis. The increased extracellular potassium and intracellular calcium causes cellular acidosis.

The cells swell due to accumulation of cytokines and other inflammatory mediators like prostaglandins leading to cytotoxic edema.[27]

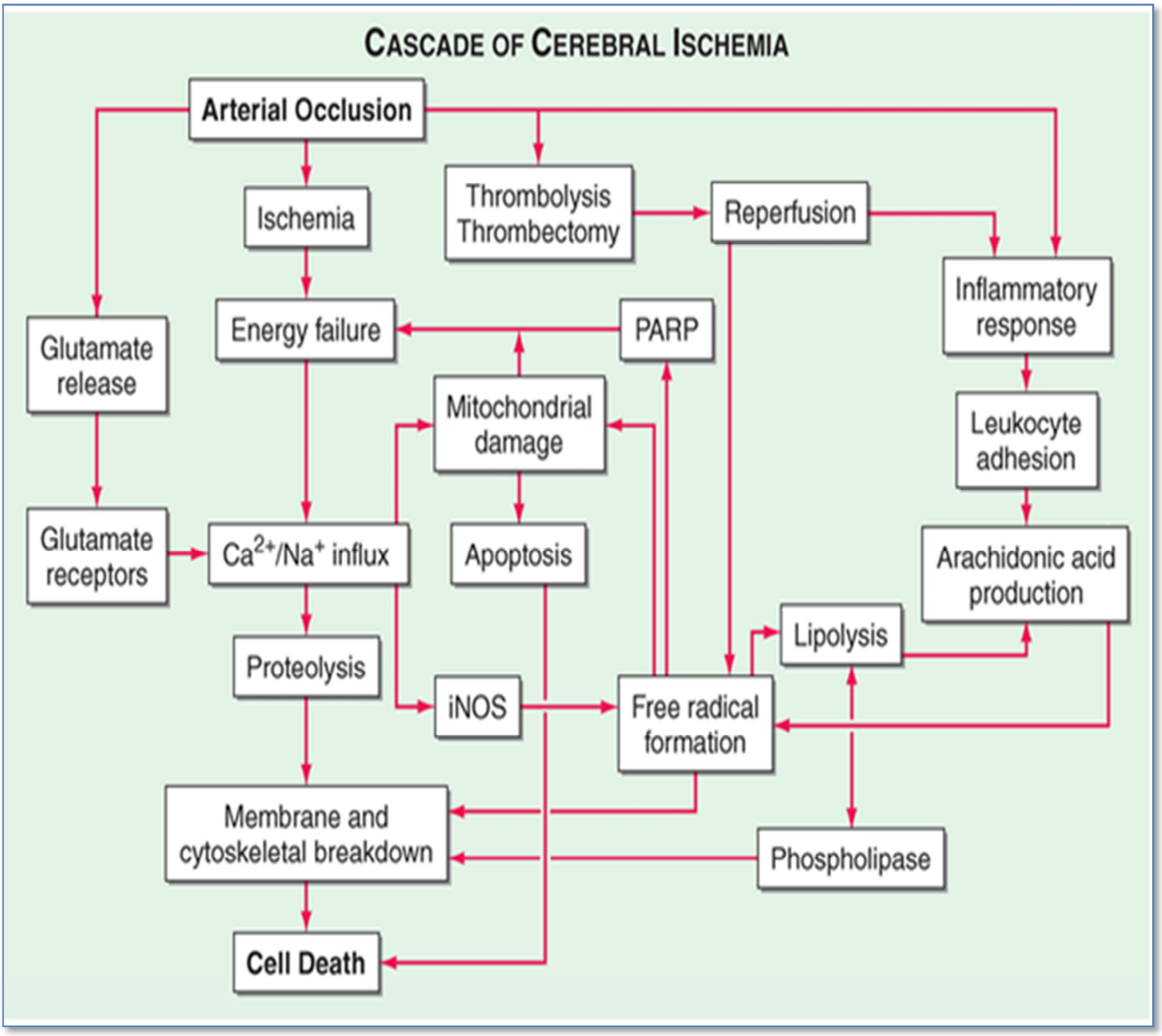
CHANGES DUE TO ALTERED METABOLIC FACTORS:

- Glutamate:

  Glutamate is a excitatory neuro transmitter that is cleared by glutamate transporters from the extracellular space. Following stroke the glutamate transporters release glutamate. Glutamate is excitotoxic, so its release causes brain damage following stroke. Glutamate also increases calcium influx leading to persistent depolarization and activation of enzymes, release of cytokines and loss of cellular integrity.

- Mitochondrial Dysfunction:

  Activation of neuronal NOS, inducible nitric oxide in glial cells lead to Mitochondrial damage and causes ischemia of the brain.



TYPES OF ISCHEMIC STROKE:

There are various classification systems for acute ischemic stroke.

The Oxford Community Stroke Project classification (OCSP, also known as the Bamford or Oxford classification) relies primarily on the initial symptoms; based on the extent of the symptoms, the stroke episode is classified as-

a) Total anterior circulation infarct (TACI).

b) Partial anterior circulation infarct (PACI).

c) Lacunar infarct (LACI).

d) Posterior circulation infarct (POCI).

These four entities predict the extent of the stroke, the part of the brain affected the underlying cause, and the prognosis.

The TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification is based on clinical symptoms as well as results of further investigations; on this basis, a stroke is classified as being due to-

a) Thrombosis or embolism due to atherosclerosis of a large artery.

b) Embolism of cardiac origin.

c) Occlusion of a small blood vessel.

d) Other determined causes.

e) Undetermined cause (two possible causes, no cause identified, or incomplete investigation).

ANTERIOR CIRCULATION STROKE (ACS):

- The major blood vessels involved in ACS are
    - Carotid Artery mainly internal carotid artery (ICA)
    - Middle cerebral artery (MCA)
    - Anterior cerebral artery
    - Anterior choroidal artery
- When ACA and MCA are occluded at the top of carotid artery – abulia or stupor / occur with aphasia, anasognosia, hemiplegia, hemianisocoria and amaurosis fugax.

Middle Cerebral Artery (MCA):

MCA involvement causes symptoms of contralateral hemiplegia, homonymous hemianopia, hemianaesthesia, gaze preference to same side and Wernicke's aphasia.

Anterior cerebral artery (ACA):

ACA involvement causes bilateral pyramidal signs, profound abulia, paraparesis or quadriparesis and urinary incontinence.

Anterior choroidal artery:

Anterior choroidal artery involvement leads to contralateral hemiplegia, homonymous hemianopia and hemianaesthesia.

Common carotid artery:

Common carotid artery involvement causes Jaw claudication.

POSTERIOR CIRCULATION STROKE (PCS):

The arteries involved are posterior cerebral artery, posterior inferior cerebellar artery, Vertebral Artery, Basilar Artery. Posterior circulation syndromes are because of emboli / atheroma formation, at the top of basilar artery.

P1 Syndrome and P2 Syndrome are due to Posterior cerebral artery occlusion. The features are

- Contralateral homonymous hemianopia with macular sparing.
- Bilateral infarction of distal PCA
- Cortical blindness

- Anton's Syndrome
- Balint's syndrome - Balint's syndrome occurs due to infarction in water shed area between MCA and PCA.
- Embolic occlusion of top of basilar artery - Bilateral signs, ptosis, pupillary asymmetry, absence of light reflex and somnolecence.
- Vertebral and Posterior ICA - Lateral medullary Syndrome, Medial medullary Syndrome.
- Hemiparesis is not the feature of vertebral artery occlusion, but quadriparesis can result from occlusion of anterior spinal artery.

INVESTIGATIONS:

CT Brain:

Brain CT scans obtained in the first several hours after an infarction generally show no abnormality, and the infarct may not be seen reliably for 24–48 hours.

MRI:

MRI reliably documents the extent and location of infarction in all areas of the brain, including the posterior fossa and cortical surface

Conventional x-ray cerebral angiography:

Conventional x-ray cerebral angiography is the gold standard for identifying and quantifying atherosclerotic stenosis of the cerebral arteries.

Ultrasound Techniques:

Stenosis at the origin of the internal carotid artery can be identified and quantified reliably by ultrasonography that combines a B-mode ultrasound image with a Doppler ultrasound assessment of flow velocity ("duplex" ultrasound). Transcranial Doppler (TCD) assessment of MCA, ACA, and PCA flow and of vertebrobasilar flow is also useful. This latter technique can detect stenotic lesions in the large intracranial arteries because such lesions increase systolic flow velocity. Furthermore, TCD can assist thrombolysis and improve large artery recanalization following rtPA administration.

Perfusion Techniques:

Both xenon techniques (principally xenon-CT) and PET can quantify cerebral blood flow. These tools are generally used for research but can be useful for determining the significance of arterial stenosis and planning for revascularization surgery. Single-photon emission computed tomography (SPECT) and MR perfusion techniques report relative cerebral blood flow.

Disability adjusted life year (DALY):

Disability adjusted life year is used to measure the global burden of disease. It's the healthy time lost by the patient due to early mortality and life with morbidity. Modified Rankin's scale is commonly used in India to evaluate DALY.[28]

Modified Rankin's Scale[29]:

It is one of the commonly used clinical outcome measures in patients with stroke

0 → No symptoms

1 → No significant disability, able to carry out all usual activities despite some symptoms

2 → Slight disability, able to look after own affairs without assistance, but unable to carry out all the previous activities.

3 → Moderate disability, requires some help, but able to walk unassisted.

4 → Moderately severe disability. Unable to attend own bodily needs without assistance and unable to walk unassisted.

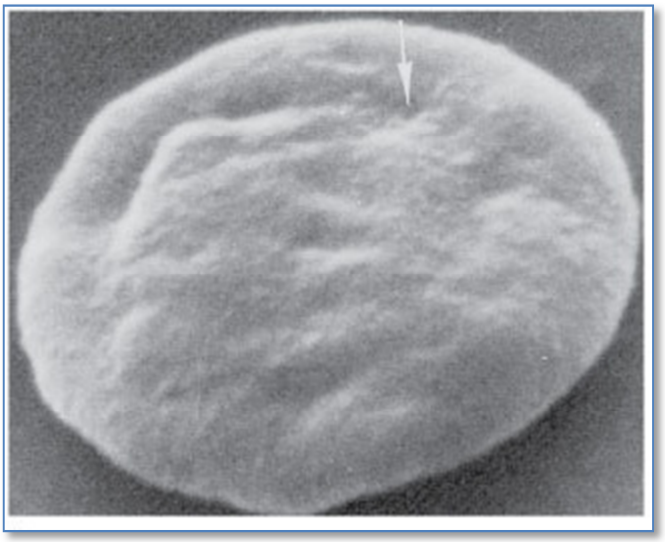
5 → Severe disability, requires constant , nursing care and attention, bed ridden and incontinent.

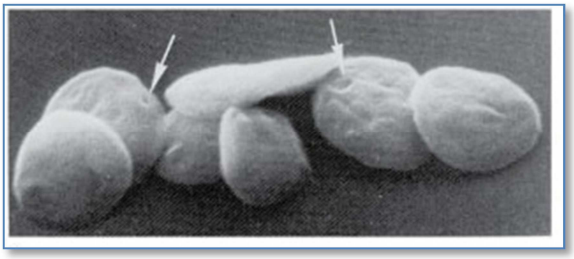
6 → Dead.

PLATELETS:

- Platelets are small, non nucleated cells with occasional reddish granules present in blood vessels.
- It was first described by Addision in 1841 as extremely minute granules in clotting blood[30].
- In 1906 it was James Horer Wright who put forth a hypothesis that platelets are derived from cytoplasm of Megakaryocytes.[31]
- Platelets are produced in yolk sac at first goes to liver and then to Bone Marrow at the time of gestation
- The half life of platelets is 7 – 10 days .Platelet production increase > 10 fold in stress.[32] Stress platelets are large, beaded in shape. Recticulated platelets are young, released from bone marrow and term reticulated refers to RNA content and in analogues to young red cells reticulocytes[33].
- 1/3rd of platelets are produced in spleen and platelet count is 150000 to 450000 / µl.

The Lentiform Shape of Circulating Platelets:





Megakaryopoiesis:

About $1x10^8$ megakaryocytes are produced in the bone marrow every day. Colony forming unit megakaryocytes develops into 3-50 mature megakaryocytes. Burst forming unit megakaryocytes develop into hundreds of megakaryocytes.

Megakaryocytes after getting released from hematopoietic stem cell undergo four stages to form platelets.

- Stage I – Megakaryoblast –

- Stage II – Basophilic megakaryocyte
- Stage III – Granular megakaryocyte
- Stage IV – Mature megakaryocyte.

About 20% of the megakaryoblast produces platelets. In stage II and III, α granules and demarcation membranes are formed. The platelet α granules contain fibrinogen, Platelet factor – 4 , Von willibrand factor and TGF β. In stage IV composition of the platelet membrane occurs.

The Megakaryocyte-platelet hemostatic axis:

The megakaryocytes are derived from hematopoietic stem cells. These are polyploidal cells, an unique feature among all the mammalian cells. This exactly means that they can redouble the chromosomal DNA content without undergoing full mitotic division. This process is known as endomitosis. Each day about 1000-2000 platelets are produced from each megakaryocyte. The measurement of platelet and megakaryocyte are closely related that they are considered as one system - Megakaryocyte platelet haemostatic axis (MKPHA).

When platelet destruction occurs in the absence of platelet production Mean platelet volume alone increases and megakaryocyte ploidy remains

unchanged.Megakaryocyte ploidy increases only when the platelet production is increased. So the regulation of ploidy and mean platelet volume are under separate hormonal control.

Physiology of Thrombopoiesis:

Thrombopoiesis is the generation of platelets from megakaryocytes. Platelet formation occurs from the plasma membrane of megakaryocyte. The process of platelet formation starts from demarcation membrane.

Demarcation Membrane:

Demarcation membrane are the extensions of plasma membrane of megakaryocyte into the cytoplasm. It divides the cytoplasm as platelet territory. The membranes provide substrate for proplatelet process to release platelets.

Proplatelet Formation:

The megakaryocytes extends slender process between the cells and the sinusoidal lumen. These are the proplatelet processes that contain nascent platelets.

The major cytokine for platelet formation is thrombopoeitin. The term Thrombopoeitin was coined in the year1958, as the primary regulator of platelet function.[34] During the development of proplatelet into the platelets,

thrombopoietin plays a crucial role. In the terminal stage cytokines helps in stimulation of the process. Activation of protein kinase Cα is necessary for the same process.

Platelet Morphology:

- The average diameter of platelet is 1.5 – 3 μm. The platelets are surrounded by glycocalix, proteins and lipids and contains sialic acid which gives negative change to the platelets in electric field. The negative surface charge prevents the resting platelets from adhering to each other .Approximately 50% of platelet lipids are present in plasma membrane.

- Phosphatidyl serine is negatively charged phospholipid present in plasma membrane. Its presence prevents inappropriate coagulation .The discoid shape of platelet is due to arrangement of microtubules below the plasma membrane.[35,36,37]

- Lysosomes have numerous enzymes especially the protein in lysosomal membrane like LAMP-1, LAMP-2.Lysosomal associated protein acts as markers of platelet release reaction.[38,39] It also contains elastase, collagenase which can accelerate the vascular injury at the site of thrombus formation.

- Dense bodies have ADP, serotonin, ATP and many other factors. ADP is the potent platelet agonist, so its release is an important factor in platelet aggregation. Platelets can uptake the oxidized LDL presented by macrophages by the release of proteins, thus accelerates atherosclerosis.

- There are two forms of Platelets
    - Resting form
    - Activated form

- The platelets may remain in Resting form as long as there is no Agonist (Thrombin). The platelets remain resting state due to
    - Negative charge and exposure to Prostacyclin in blood vessel .At the same time even a minimal agonist stimulation can activate the platelets.

FUNCTIONS OF PLATELETS:

- Maintains hemostasis
- Angiogenesis and promote wound healing

Platelet Function:

- Platelet Adhesion: Whenever vascular endothelial injury occurs, platelets get adhered to the vessel wall through Von Willibrand factor.
- Platelet Aggregation: The platelets get aggregated by the activation of Gp IIb / IIIa receptor.
- Secretion: Platelets release growth factor, procoagulants and nucleotides and forms clot leading to formation of platelets plug and is stabilized by fibrin mesh.

Clot Retraction:

Clot retraction is the process by which the clot that is formed after vascular injury retracts over time. This process helps the platelet rich thrombi to withstand the shear forces in vessel walls.

PLATELET INDICES:

Quantitative index is Platelet count. Qualitative index is Mean platelet volume that measures the activity and function of platelets. Others include Platelet distribution width, Platelet large cell ratio. Platelet mass is the product of Mean platelet volume and platelet count and its inversely proportional to the bleeding time.

MEAN PLATELET VOLUME:

Mean platelet volume is used to calculate the average size of platelets in the blood. It is the indicator of platelet function and activity. The platelets that are newly released from bone marrow are the young platelets that are larger, contains more proteins (Platelet factor-4).Increase in MPV during increase in platelet production or destruction is controlled by release of various cytokines like Interleukin6,3 and thrombopoietin.

Normal Mean Platelet Volume:

The normal mean platelet volume ranges between 7.5*fl* to 10.5 *fl.*

Conditions with high MPV and low platelet count**:**

- Heterozygous thalassemia
- Iron deficiency anemia
- Increased platelet turn over
- Bernald soulier syndrome

Conditions with high MPV and high Platelet count**:**

- Myeloproliferative disorder
- Inflammation
- Iron deficiency anemia

Conditions with normal MPV and high platelet count**:**

- Sickle cell anemia
- CML
- Inflammation
- Infections

Conditions with low MPV:

- Chronic renal failure
- Myelosuppresive drugs
- Marrow hypoplasia

- Aplastic anemia
- Sepsis
- Big spleen syndrome
- X linked congenital macrothrombocytopenia
- Idiopathic Thrombocytopenic Purpura

MPV AND AGE:

It was an earlier concept that mean platelet volume decreases with age. But the recent studies have shown that MPV is determined during thrombopoesis itself by its precursor megakaryocyte in the bone marrow.[40,41]

MPV AND GENDER:

MPV is likely to be higher in women than in men. It might be due to different hormonal profile or it may be due to compensatory mechanism for menstrual blood loss in women. Study conducted by Kiewicz and Kemona et al in women of 60 years of age concluded that there is no significant statistical difference in MPV between men and women.[42]

MPV IN SMOKERS:

MPV is elevated in elderly with history of smoking. Smoking increases the rate of atherosclerosis, thereby increasing the platelet consumption and in turn the new platelets formed are larger in size and thus the MPV is elevated.[43]

MPV IN ALCOHOLICS:

The significance of mean platelet volume in alcoholics is still controversial but the life style modification has been associated with decreased MPV.[44]

MPV IN ISCHEMIC STROKE:

Platelets are non-nucleated structure with little or no capacity to synthesize protein. The hemostatic function of platelet is established before thrombopoiesis itself by megakaryocytes , the precursor of platelets. In certain pathological condition like acute ischemic stroke the MPHA axis is altered leading to formation of hyperfunctional[45] platelets that leads to thrombosis causing acute ischemic stroke. It is still not clearly concluded that this hyperfunctional platelets are produced before or after stroke as a consequence.[45] And certain risk factors like Diabetes, hypertension leads to some degree of platelet activation preceeding stroke, that once the event occurs it gets aggrevated.[45]

Studies conducted by S.Greisenegger et al a cross sectional study, done at 8 neurological centres in Austria, Vienna. with 1322 patients. For 846 cases. MPV was determined and other 476 cases MPV was not determined. Modified Rankin's Scale was applied in 776 (92%) for whom MPV was done. Multivariate analysis performed by binary logistics regression analysis after adjusting for confounding factors conclude that MPV in those within the highest quintile had 2.6 times unadjusted risk of suffering a severe stroke (95% CI, 1.6 – 4.1; P < 0.001). Same MPV and modified Rankinscale compared after 3 months after controlling age and sex, MPV was associated with worse outcome. (score 3-6) – odds ratio 2.2, 95% CI, 1.1 to 4.5, p = 0.029 . More likely the results suggest increase in MPV associated with worst outcome of stroke.[46]

Philip Bath et al conducted PROGRESS TRIAL. In this 6105 patients were included within 5 years of stroke. Selected patients had taken 4-6 weeks of peridopil, an antiplatelet drug like Asprin. The study concluded that the difference in MPV between the patients on antiplatelets and off the drug is small (≤0.3*fl*). 400 strokes were recorded in the follow up period. 301 were ischemic, rest ICH and few were unknown type. Stroke rate was greater in patients with higher MPV (P for trend across fifth of MPV = 0.01) and ischemic stroke alone (p=0.01), there was no evidence of any difference in patients on single or combination of drug therapies.[47]

O Malley et al studied 58 stroke patients in a geriatric population. Platelet variables were measured within 48 hours and after 6 months of ischemic stroke and compared with controls. MPV was higher in acute stroke (11.3 with 10.1 *fl* in control subjects, $p < 0.01$, student's t test). Repeated measurements did not show significant changes at 6 months. Platelet change did not relate to outcome[48].

There is one way of possibility that MPV have changed even before stroke due to some risk factors,and further studies are warranted to analyze this.

Mayda et al studies 692 patients with ischemic stroke and observed MPV and PC were independent risk factors for ischemic stroke ($p=.0007$, odds ratio = 0.866, 95% confidence interval). Ischemic group MPV ($p = 0.013$, OR = 1.02). 95% of CI associated with worse outcome.[49]

MPV AND HYPERTENSION:

In systemic hypertension there is platelet activation and MPV is found to be increased. In study conducted by Varole et al in 87 Pre hypertensive patient, 30 hypertensive patients, the MPV values were significantly higher in both (8.4 ± 0.8 and 8.8 ± 0.7 Versus 7.9 ± 0.5 *fl* $P < 0.05$ and $P < 0.001$ respectively). Hypertensives had increased MPV than Pre hypertensives. Presence of Hypertension is an independent parameter in prediction of high MPV.[50]

MPV AND DIABETES MELLITUS:

Diabetes is a global pandemic. Platelets function or activation can lead to athero thrombosis. The platelets itself can cause vascular injury by three mechanism like triggering of arterial thrombosis, microemboli formation in capillaries and aggrevation of local progression of vascular disease.

Platelet activation in DM occurs by 3 ways

1. The immature young platelets are synthesized in bone marrow.
2. The metabolic changes in DM , have impact on platelets. They get activated with that of metabolic changes.
3. Vascular damage triggers the activation of platelets in DM.

Increased MPV directly have positive correlation with that of Glycoprotein GpIIb and GpIIb/IIIA receptors on plasma membrane, the Thromboxane synthesizing capacity and granule content of platelets.

The study conducted by Thomas Alex Kodiatte et al in 300 type 2DM and 300 Non DM patients, the MPV was higher in Diabetes is (8.29 ± 0.74 *fl* Versus 7.47 ± 0.73 *fl*) ($p = 0.001$) than non diabetics.

MPV showed a significant positive correlation with blood sugar values (both FBS, PPBS) and HbA1C. The elevated MPV may be the cause or consequence of vascular complication in diabetes[51].

MPV IN HYPERLIPIDEMIA:

Study conducted by Coban et al shared that the baseline MPV was higher in dyslipidemic patients (8.4 ± 1.2 *fl* VS 8.1 ± 0.10 *fl* $P < 0.0005$).[52]

MPV AND METABOLIC SYNDROME:

MPV is emerging as an atherothrombotic factor. Study conducted by Shah B et al as retrospective study in national health and nutrition examination survey found that MPV was significantly elevated in abdominal obesity ($P = 0.03$) and low HDL ($P = 0.04$). The metabolic syndrome was defined by National Cholesterol Education Program Adult Treatment Panel III definition.[53]

MPV AND ANTIPLATELET DRUGS:

The essential step in hemostasis is platelet aggregation which is involved in many pathological process like ischemic stroke, TIA, atherosclerosis. Aspirin irreversibly inhibits platelet aggregation by inhibition of cyclooxygenase and TXA2 pathway. It is used in secondary prevention of stroke and primarily in TIA. Stephen Erhart conducted study on influence of Asprin on platelets. In the studies conducted it

was concluded that Asprin does not influence MPV level before or after the stroke.[54]

MPV AND ISCHEMIC HEART DISEASE:

Large platelets act as the risk factor in developing coronary occlusion, leading to acute coronary syndrome. Studies conducted by M M Khandekar et al in 210 cases of acute coronary syndrome, the MPV, PWD , P-LCR were significantly elevated in patients with acute myocardial infarction and unstable angina.[55]

METHODOLOGY

SOURCE OF DATA:

The study was conducted on patients with Ischemic stroke of first episode for the patients admitted in Medical wards in Institute of Internal Medicine at Rajiv Gandhi Government General Hospital, Chennai.

Study Design : Case control study

Sample Size : 100 patients

METHOD OF COLLECTION OF DATA:

After obtaining consent the patients and controls were subjected to detailed history, clinical examination and investigations as per the proforma.

The following criteria were applied for selection of patients in the study group.

Inclusion Criteria :

First episode of Ischemic Stroke (confirmed by imaging studies) with or without risk factors.

Controls : Normal people

Exclusion Criteria : 1. Hemorrhagic stroke,

2. Recurrent stroke,

3. Patient already on antiplatelet drugs,

4. Thrombocytopenia.

5. Known case of hereditary disorders of large platelets

INVESTIGATIONS:

All the patients and controls underwent the following investigations.

- Complete hemogram
- Fasting and post prandial blood sugars
- Fasting lipid profile
- Electrocardiogram
- Echocardiography
- Imaging studies for patients alone (CT , MRI)

For the measurement of Mean Platelet Volume 2ml of Blood sample was collected from the antecubital vein using 2cc syringe and transferred to an EDTA test tube and analyzed in an automated cell counter Sysmex KX21 Blood samples were taken in patients with ischemic stroke at the time of admission, after one week and at the end of 1month.

CRITERIA/CASE DEFINITION FOR CLASSIFYING THE PATIENTS AND CONTROLS:

(1) **DIAGNOSIS OF DIABETES MELLITUS:**

(a) Fasting Plasma Glucose > 126mg/dl and 2 Hours post prandial plasma glucose > 200mg/dl or HbA1c ≥ 6.5.

(b) Known cases of type 2 Diabetes Mellitus taking/not taking medications.

(2) **HYPERTENSION:**

(a) Blood Pressure > 140/90 mm of Hg recorded in sitting posture on each of 2 or more visits.

(b) Known hypertensive patients taking/not taking medications

(3) **DYSLIPIDEMIA:**

(a) Total cholesterol ≥200 mg/dl.

(b) Known cases of dyslipidemia with or without medications.

(4) **CARDIOVASCULAR DISEASE:**

(a) History of Chest pain, breathlessness on exertion, prior myocardial infarction, congestive cardiac failure.

(b)ECG features

- Left ventricular hypertrophy.
- Ischaemic heart disease – ST – T changes
- Features of old myocardial infarction.

(c) Echocardiography (in selected situations only)

- Regional wall motion abnormalities (RWMA)
- Decreased Ejection Fraction

(5) **STROKE:**

History, clinical examination and imaging studies (CT/MRI) for stroke was done.

OBSERVATIONS AND RESULTS

SAMPLE:

The study was conducted at the Rajiv Gandhi Government General Hospital Chennai. 100 cases who met the inclusion criteria and 50 age and sex matched controls were included in the study after obtaining informed consent.

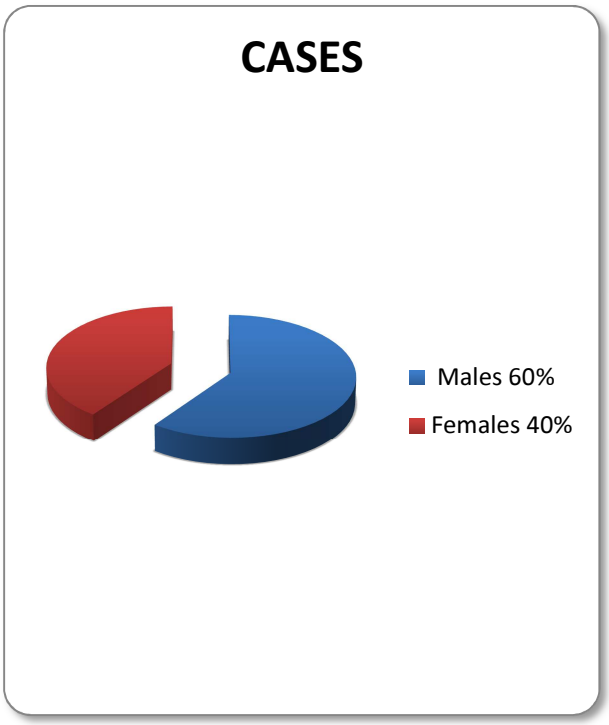
DATA ANALYSIS:

The statistical analysis was done using GraphPad Prism version 6.00 for Windows, GraphPad Software, La Jolla California USA. MS Excel and Word were used to generate tables and graphs.

TABLE 1: SEX DISTRIBUTION

Males constituted 60 % of the cases and controls and the remainder 40 % were females.

SEX	CASES		CONTROLS	
	Number	Percentage	Number	Percentage
Male	60	60	30	60
Female	40	40	20	40
Total	100		50	



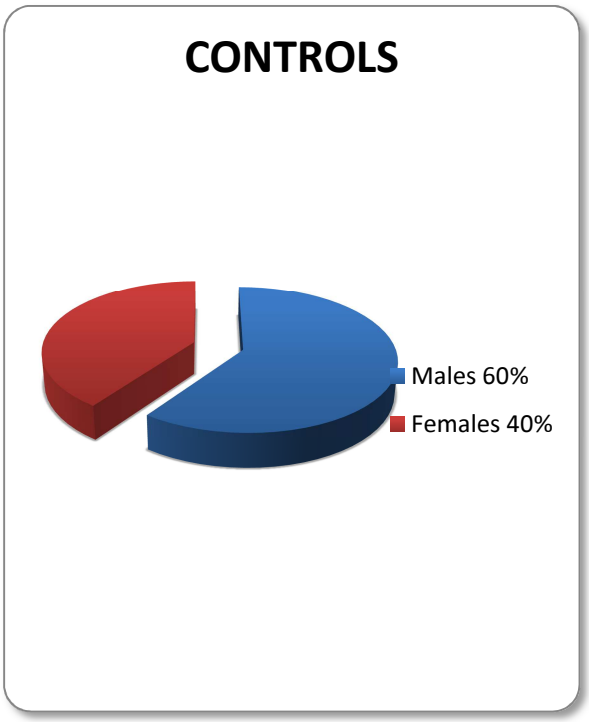


TABLE 2: AGE DISTRIBUTION

The mean age of cases was 53.49 years and mean age of controls was 54.12 years. The differences in the mean age of cases and controls was not significant (p value > 0.05).Thus cases and controls were matched for their age.

AGE DISTRIBUTION (Yrs)	CASES	CONTROLS
31 – 40	16	8
41 – 50	28	14
51 – 60	28	14
61 – 70	20	10
71 – 80	8	4
Mean ± SD	53.49 ± 11.33	54.12 ± 12.09
Standard Error of mean	1.13	1.71
P value (Unpaired t test)	0.76 (Not significant)	

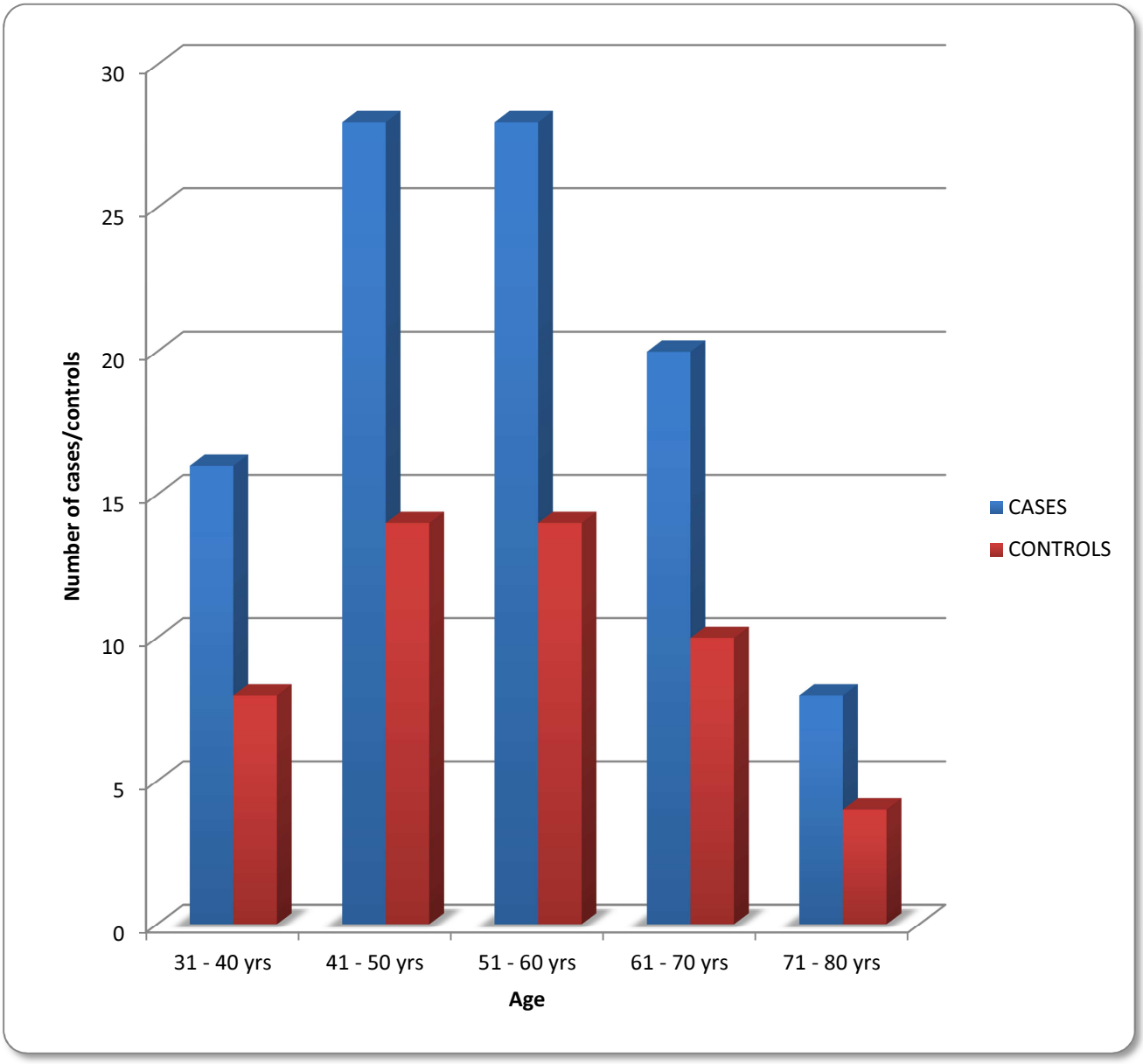

30
25
20
15
10
5
0
Number of cases/controls
31 - 40 yrs
41 - 50 yrs
51 - 60 yrs
61 - 70 yrs
71 - 80 yrs
Age
CASES
CONTROLS

TABLE 3: AGE WISE SEX DISTRIBUTION

The female patients (mean 60.08 years) were significantly older than male patients (mean 49.10 years) with a p value < 0.0001. Most of the male patients were in the age group of 31 – 50 years whereas majority of female patients were in age group of 51 – 70 years.

AGE DISTRIBUTION (yrs)	MALES	FEMALES
31 – 40	16	0
41 – 50	23	5
51 – 60	13	15
61 – 70	5	15
71 - 80	3	5
Mean ± SD	49.10 ± 10.73	60.08 ± 8.83
Standard Error of Mean	1.40	1.39
P value (Unpaired t test)	<0.0001 (Significant)	

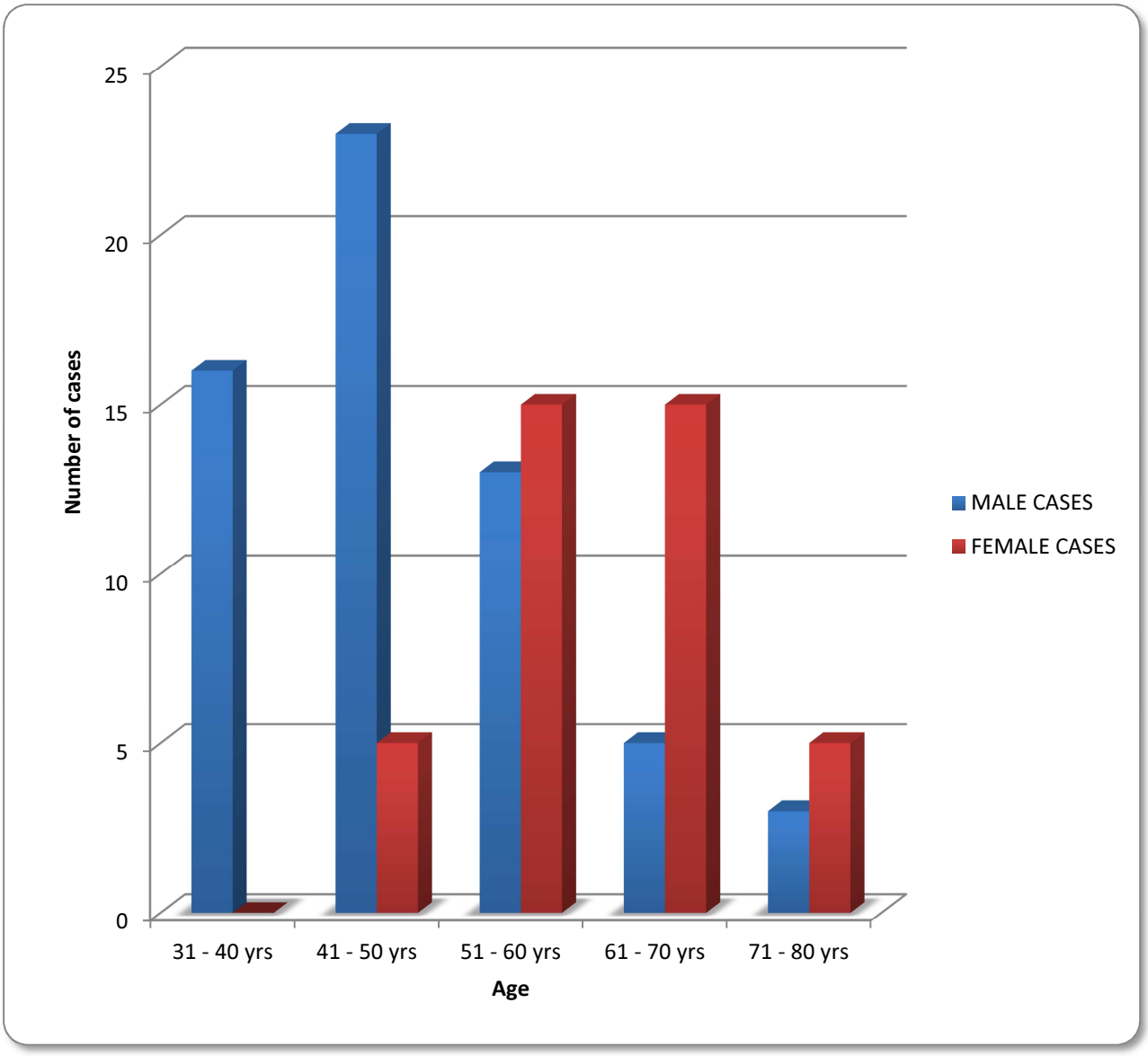
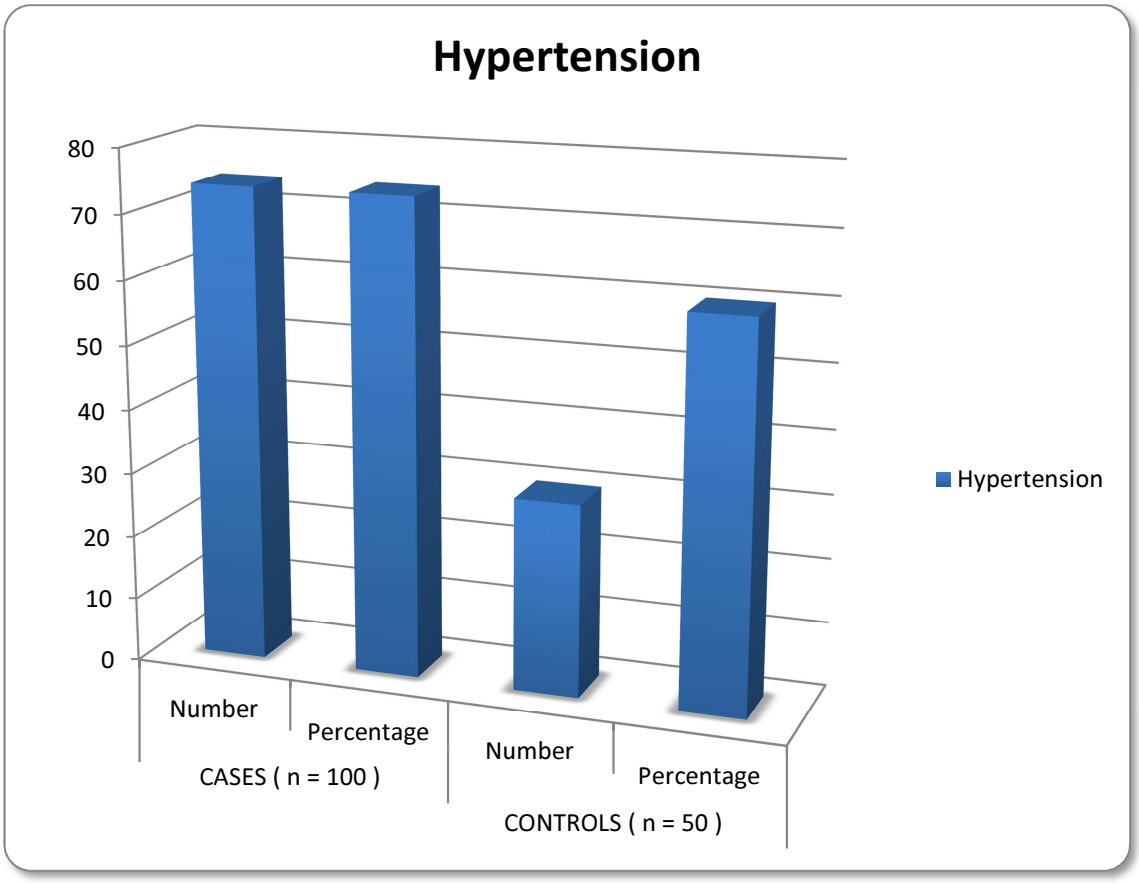

25
20
15
10
5
0
Number of cases
31 - 40 yrs
41 - 50 yrs
51 - 60 yrs
61 - 70 yrs
71 - 80 yrs
Age
MALE CASES
FEMALE CASES

TABLE 4: RISK FACTORS IN CASES AND CONTROLS

a) Hypertension:

Hypertension is the most common risk factor in both cases and controls occurring around 74% and 60% respectively.

RISK FACTOR	CASES (n = 100)		CONTROLS (n = 50)	
	Number	Percentage	Number	Percentage
Hypertension	74	74	30	60



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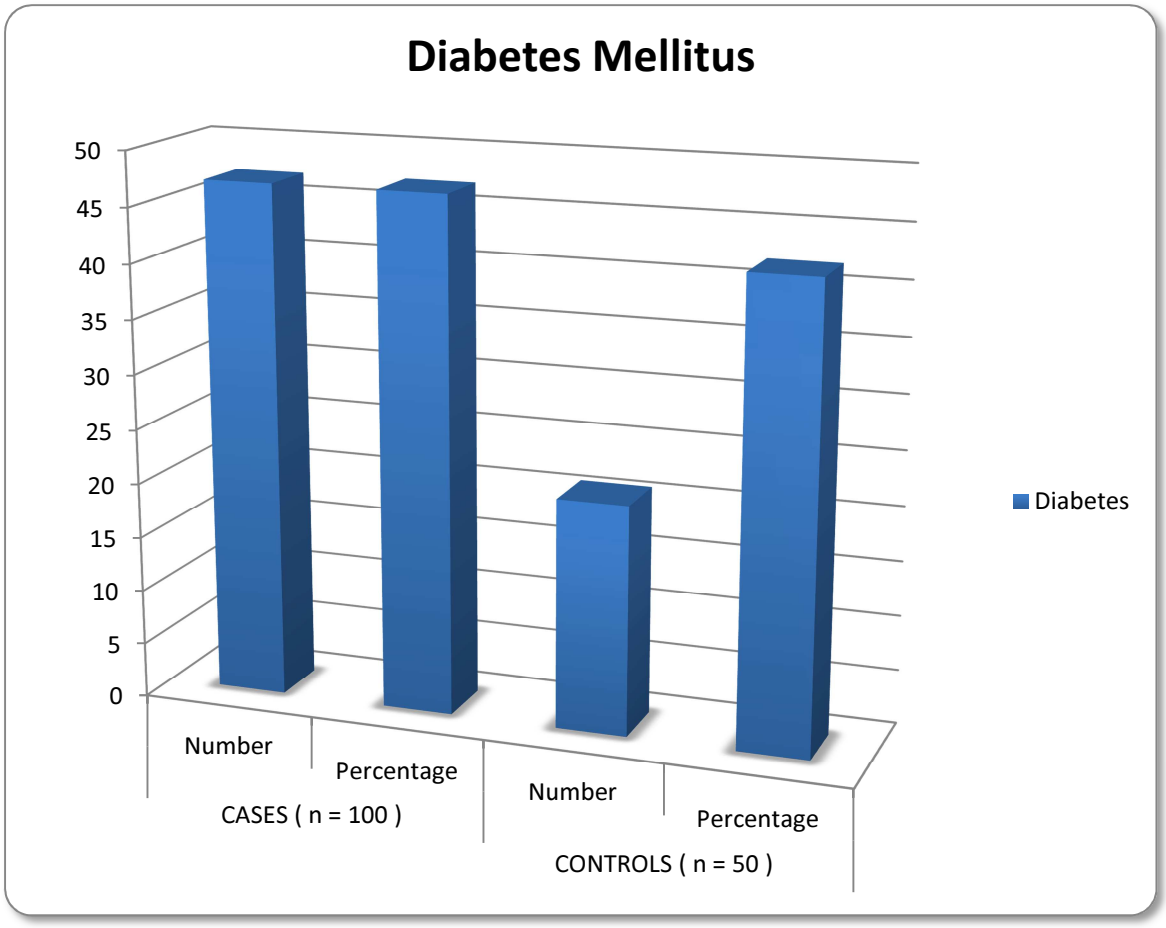
b) Diabetes Mellitus

Diabetes Mellitus as a risk factor in cases and control were 47% and 42 % respectively.

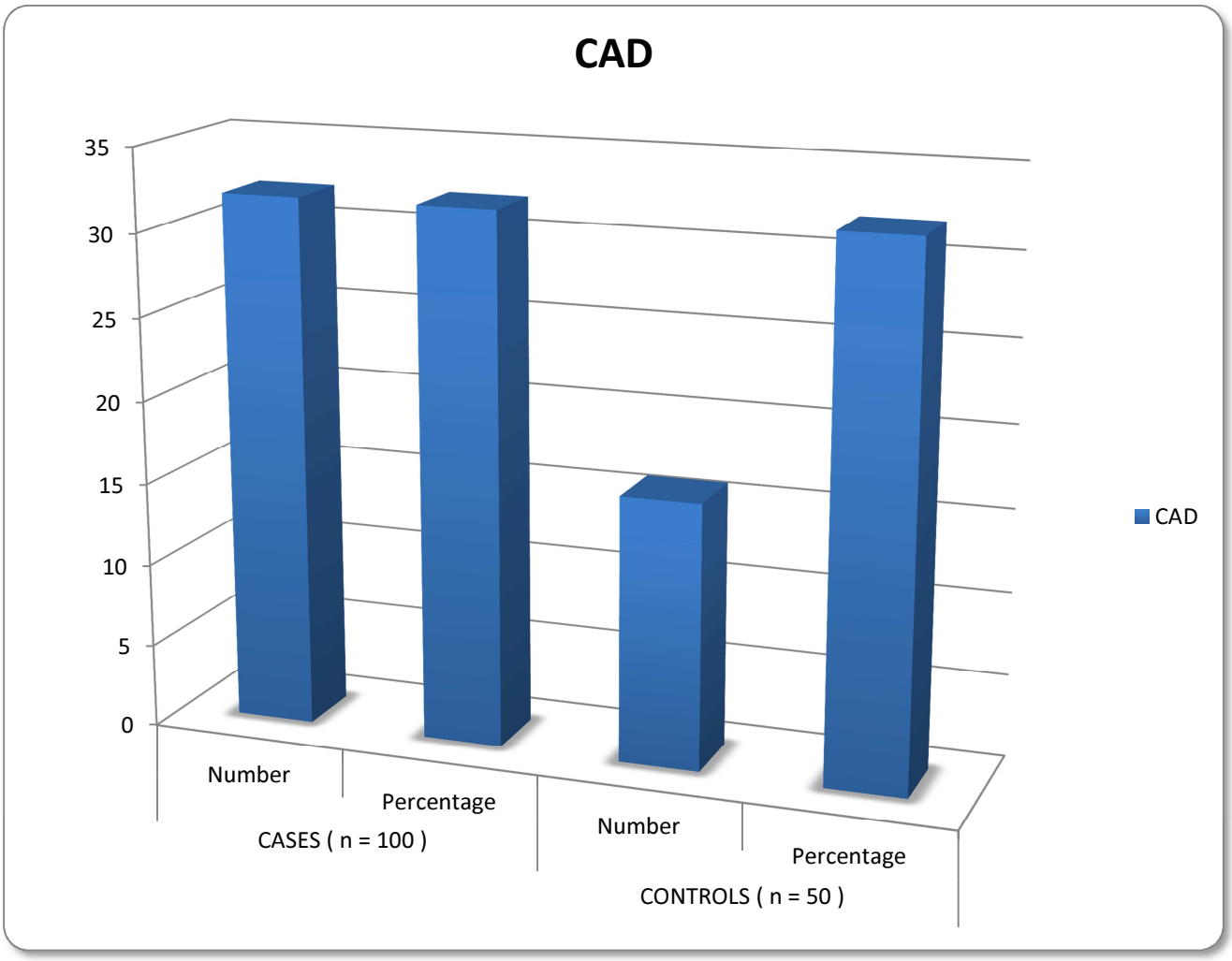
RISK FACTOR	CASES (n = 100)		CONTROLS (n = 50)	
	Number	Percentage	Number	Percentage
Diabetes	47	47	21	42



c) Coronary Artery Disease:

CAD as a risk factor in cases and control were 32% and 32 % respectively.

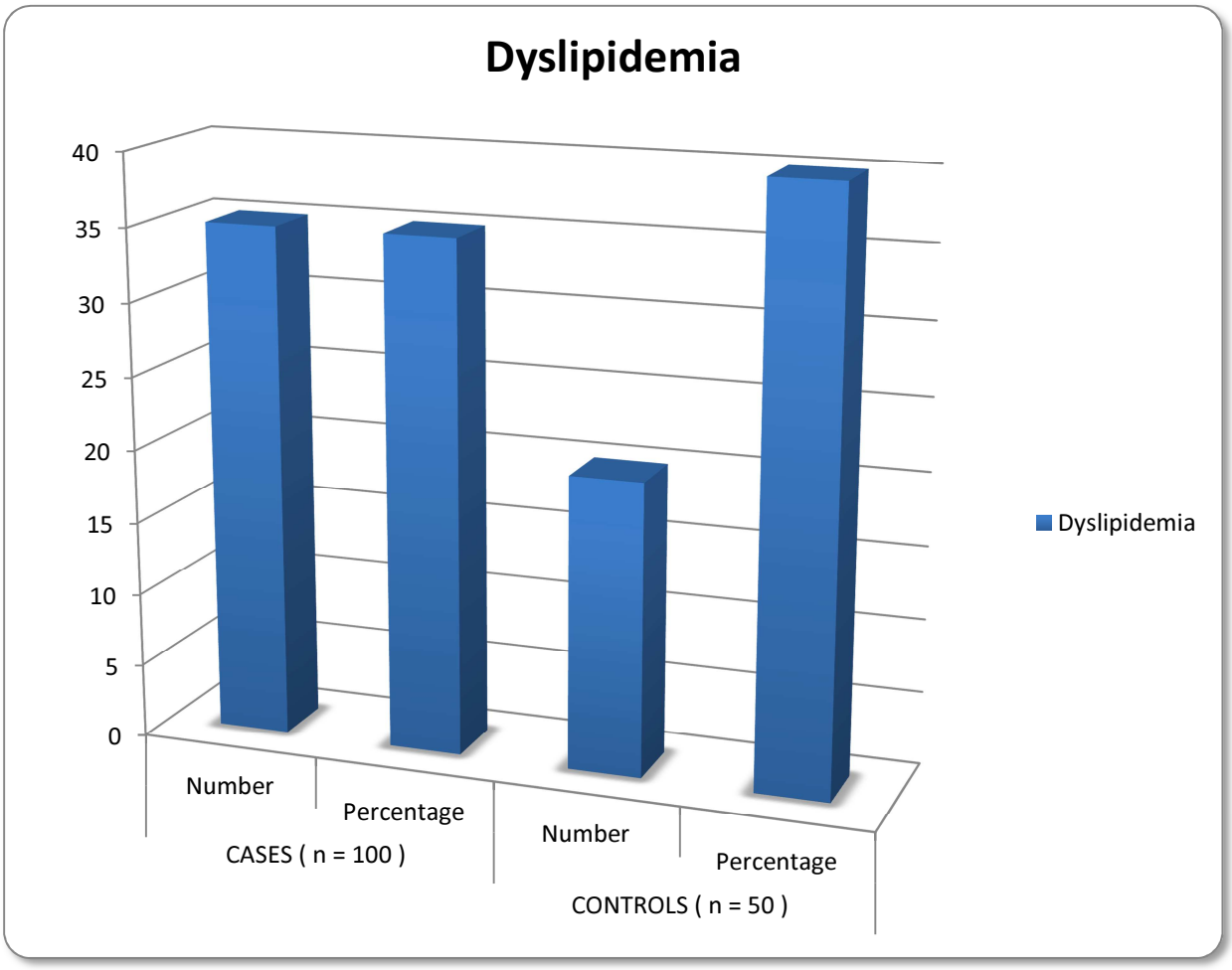
RISK FACTOR	CASES (n = 100)		CONTROLS (n = 50)	
	Number	Percentage	Number	Percentage
CAD	32	32	16	32



d) Dyslipidemia:

Dyslipidemia as a risk factor in cases and control were 35% and 40 % respectively.

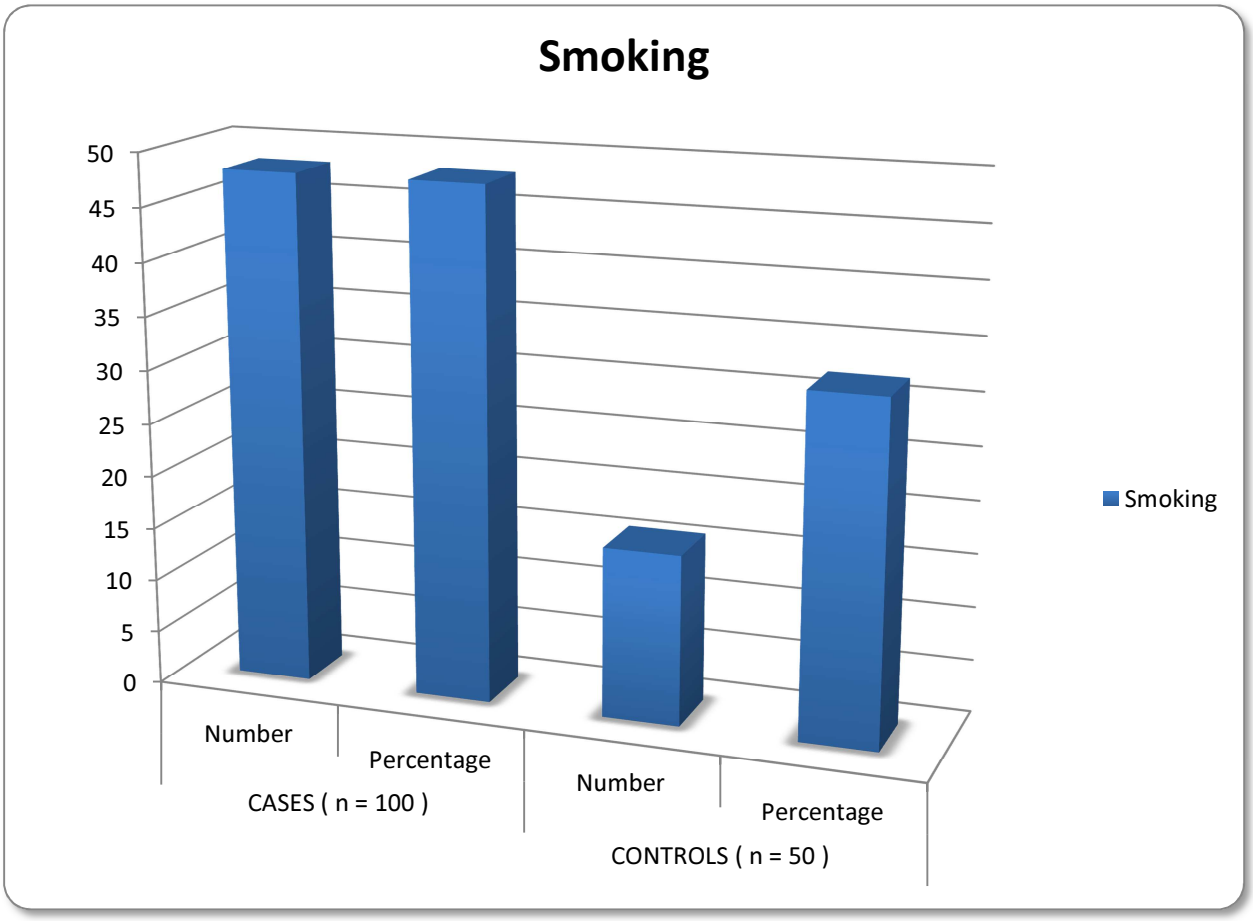
RISK FACTOR	CASES (n = 100)		CONTROLS (n = 50)	
	Number	Percentage	Number	Percentage
Dyslipidemia	35	35	20	40



e) Smoking:

Smoking is the second common risk factor next to SHT and Smoking as a risk factor in cases and control are 48% and 32 % respectively.

RISK FACTOR	CASES (n = 100)		CONTROLS (n = 50)	
	Number	Percentage	Number	Percentage
Smoking	48	48	16	32



f) Alcohol:

Alcohol as a risk factor in cases and control are 45% and 24 % respectively.

RISK FACTOR	CASES (n = 100)		CONTROLS (n = 50)	
	Number	Percentage	Number	Percentage
Alcohol	45	45	12	24

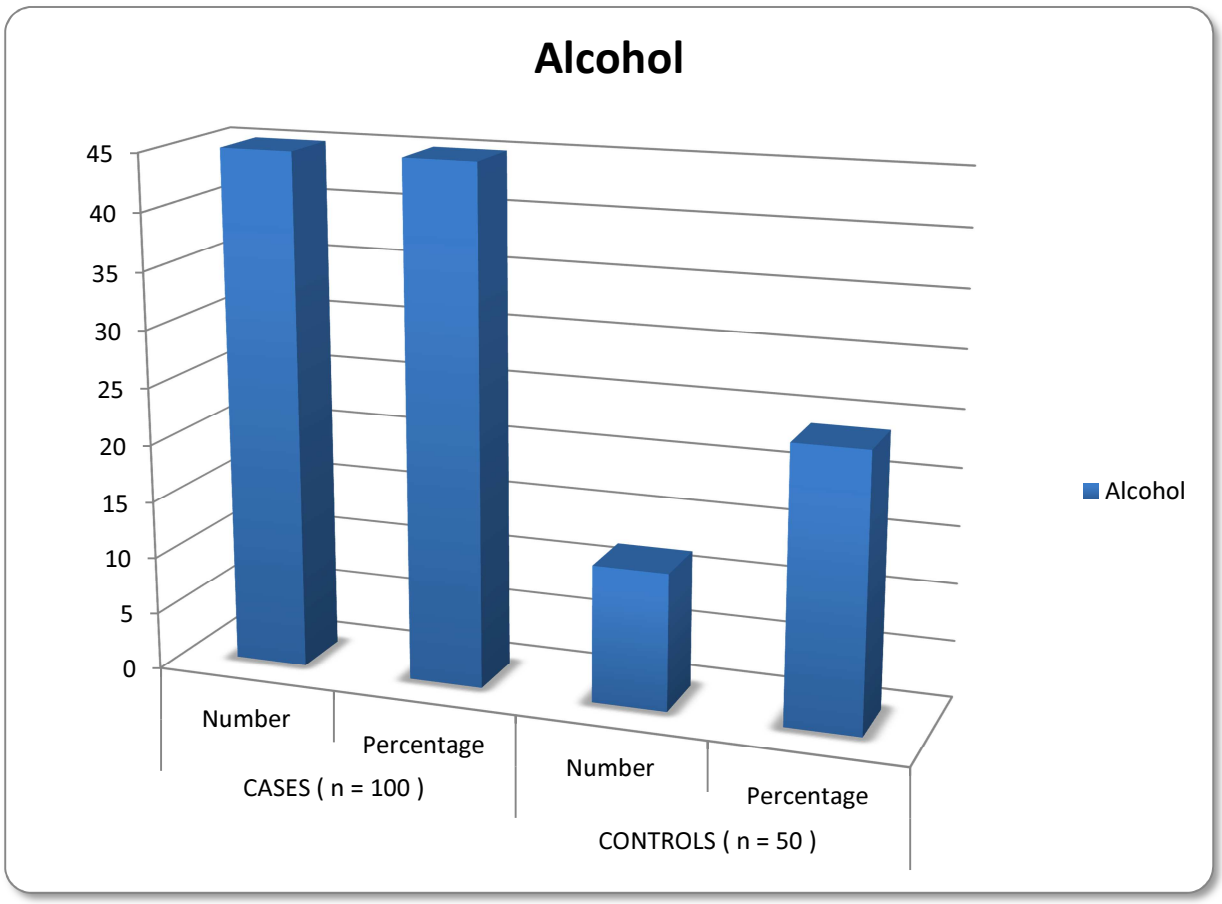


TABLE 5: INFARCT TERRITORY

The most common patterns were the tempero - parietal and parietal infarcts followed by corona radiata infarcts. The MCA territory was predominantly involved around 94 %. This was followed by involvement of posterior circulation and combined MCA and ACA territory – 3 % each.

TERRITORY	CASES
MCA	94
VERTEBRAL / BASILAR ARTERY	3
MCA + ACA	3

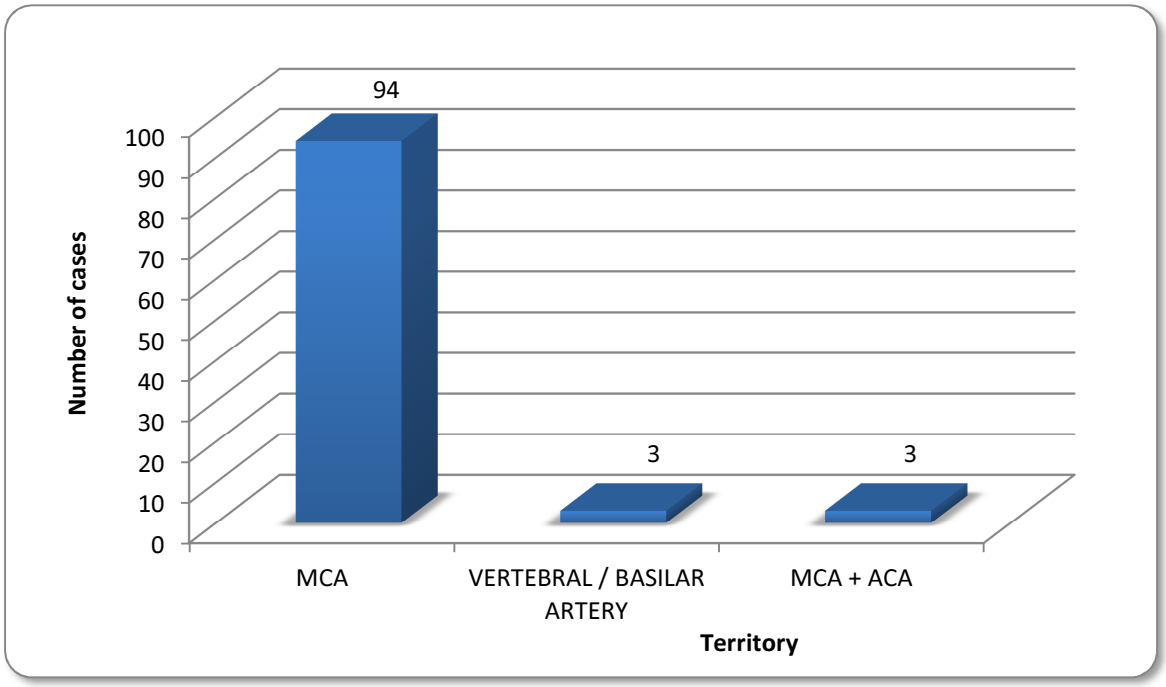


TABLE 6: OUTCOME OF THE PATIENTS – MODIFIED RANKIN SCALE

The clinical outcome of the patients was assessed using modified Rankin Scale. The scale is from 0 – 6. A score of 0 implies perfect health with no symptoms, whereas a score of 6 implies death. 26% of patients had a score of 2 and 18% had a score of 3. 19% had no symptoms. 8% of patients did not survive.

MODIFIED RANKIN SCALE	PERCENTAGE OF PATIENTS
0 (No symptoms)	19
1	14
2	26
3	18
4	9
5	6
6 (Death)	8

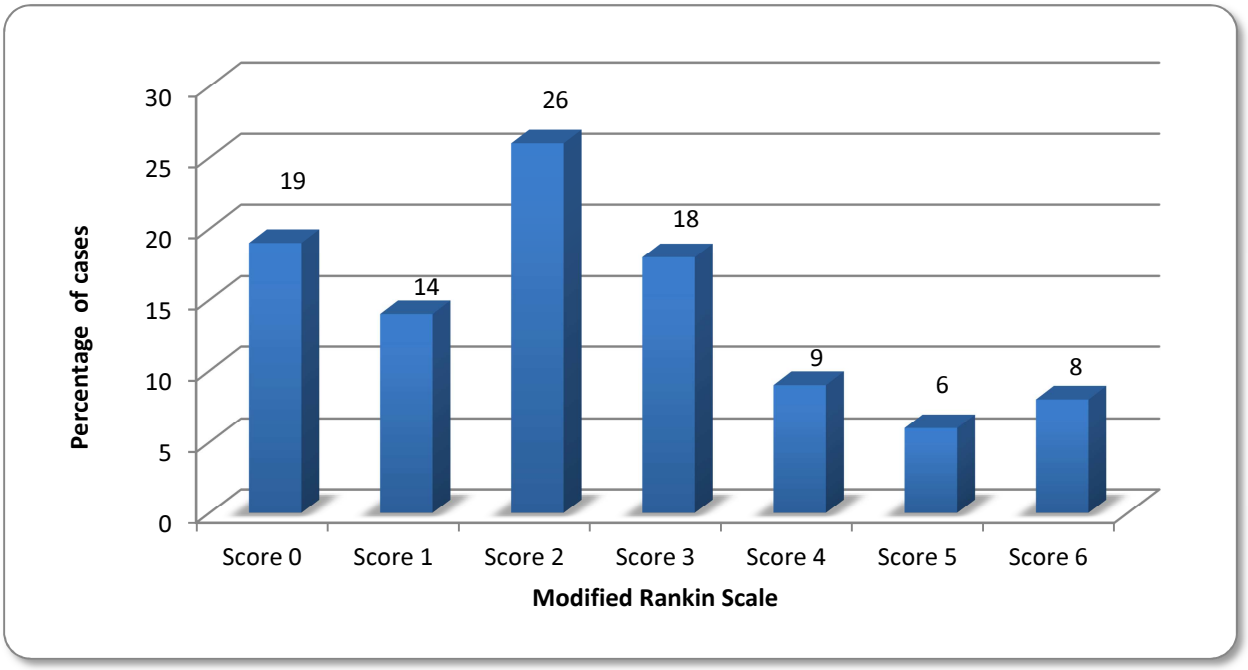


TABLE 7: COMPARISON OF PLATELET COUNTS IN CASES AND CONTROLS

The platelet counts were slightly lower in the stroke patients compared to controls but this difference was statistically not significant.

PLATELET COUNT(x 10^5 cells/cumm)	CASES (n=100)	CONTROLS (n=50)
Mean	1.84	1.93
Standard Deviation	0.27	0.27
Standard Error of Mean	0.027	0.039
P value	0.124	

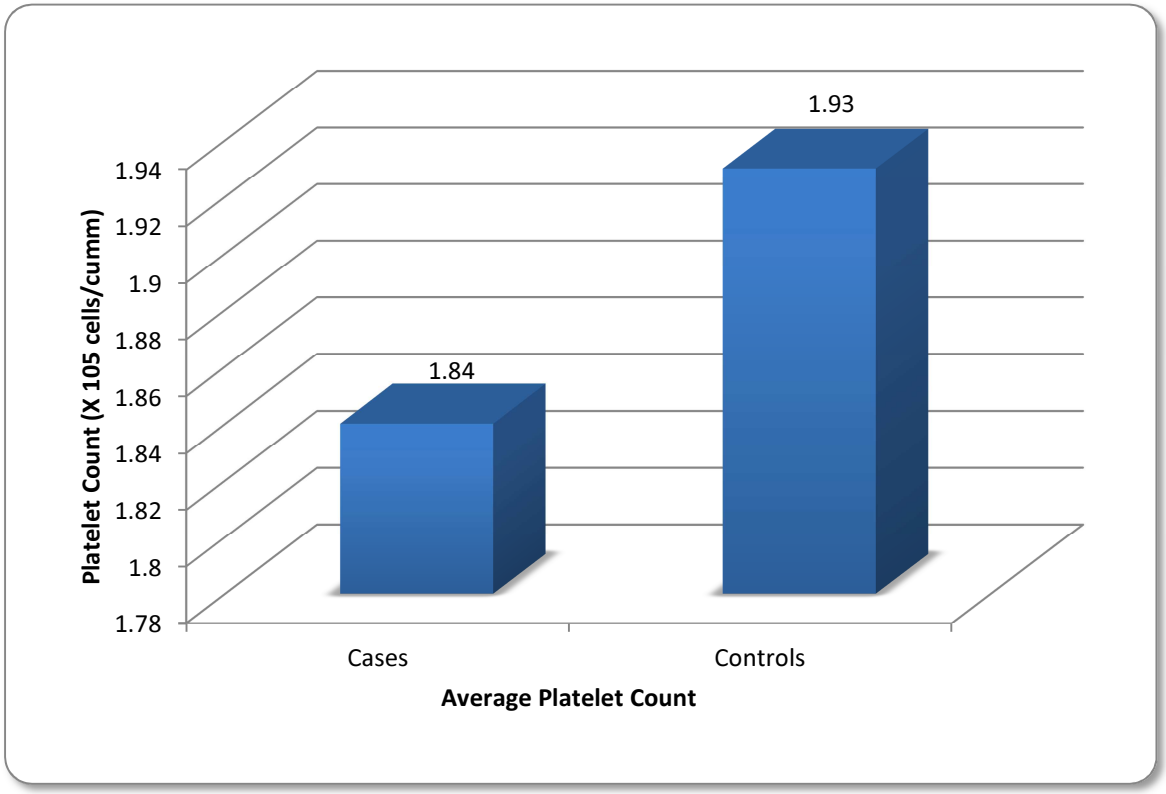


TABLE 8: COMPARISON OF MEAN PLATELET VOLUME IN CASES AND CONTROLS

The mean platelet volume in stroke patients was significantly higher than controls. The p value was less than 0.0001. There was no significant differences in mean platelet volumes on day1, day7, day28 implying that platelet volumes tend to be elevated for some time after stroke.

Another implication is that Aspirin does not alter the platelet volume over a short duration of 4 weeks.

MEAN PLATELET VOLUME(in Fl)	CONTROL	CASES		
		DAY 1	DAY 7	DAY 8
Mean	9.29	12.28	12.30	12.27
Standard Deviation	0.59	2.55	2.50	2.57
Standard Error of Mean	0.08	2.5	2.5	2.5
Confidence Intervals	9.12-9.46	11.77-12.79	11.77-12.76	11.78-12.81

Comparison of Mean Platelet Volume	P valve (Unpaired T test)	Inference
Controls versus Cases(day1)	< 0.0001	Significant
Day1 versus Day7	0.98	Not significant
Day1 versus Day28	0.92	Not significant

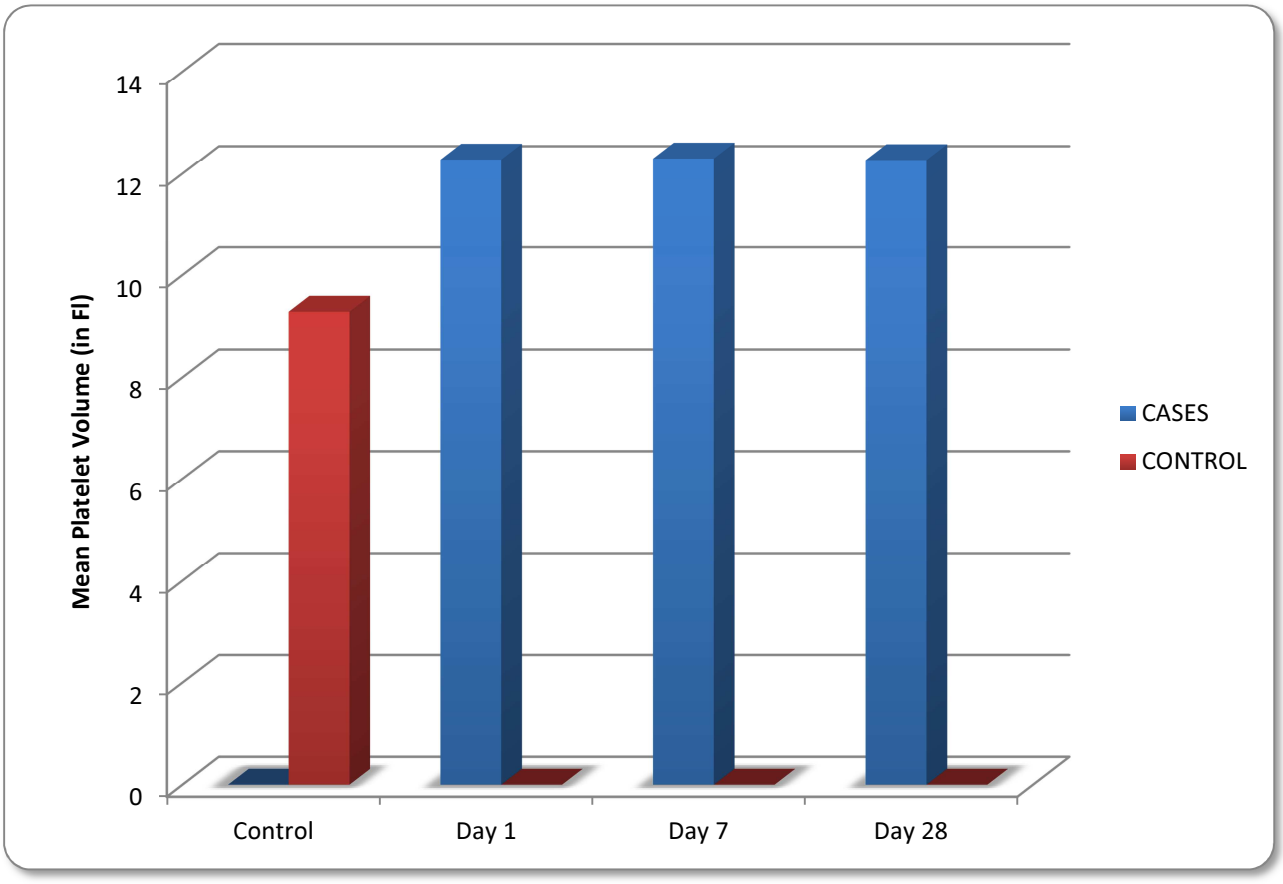


TABLE 9: COMPARISON OF MEAN PLATELET VOLUME IN MALE AND FEMALE

In our study there were no significant differences in mean platelet volume among males and females in both cases and controls.

MEAN PLATELET VOLUME	MALE		FEMALE	
	CASE	CONTROL	CASE	CONTROL
Mean	12.27	9.20	12.25	9.42
Standard Deviation	2.56	0.59	2.54	0.57
Standard error of mean	0.33	0.10	0.40	0.12
P value	Male Controls versus Female Controls - 0.20 (Not significant) Male Cases versus Female Cases - 0.97 (Not significant)			

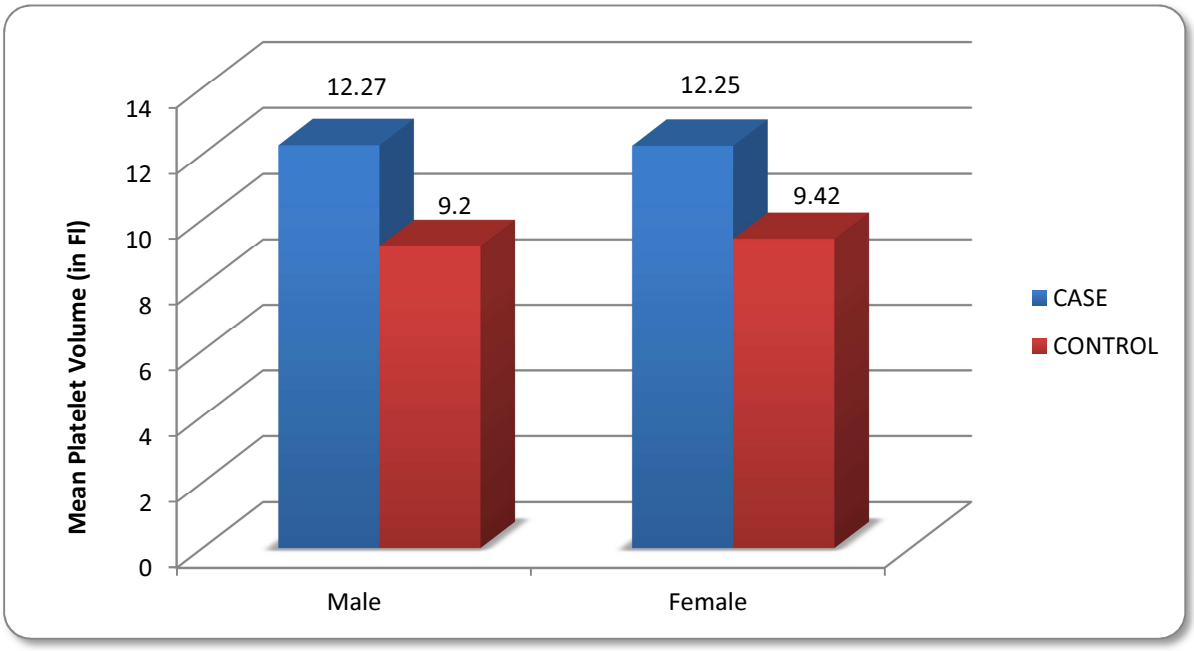


TABLE 10: MEAN PLATELET VOLUME AND AGE

There was no significant alteration in mean platelet volume with ageing.

MEAN PLATELET VOLUME	AGE ≥ 60 YEARS		AGE < 60 YEARS	
	CASE	CONTROL	CASE	CONTROL
Mean	12.76	9.36	12.72	9.24
Standard Deviation	2.42	0.54	2.77	0.62
Standard error of mean	0.30	0.12	0.48	0.12
P value	Controls - 0.49 (Not significant) Cases - 0.22 (Not significant)			

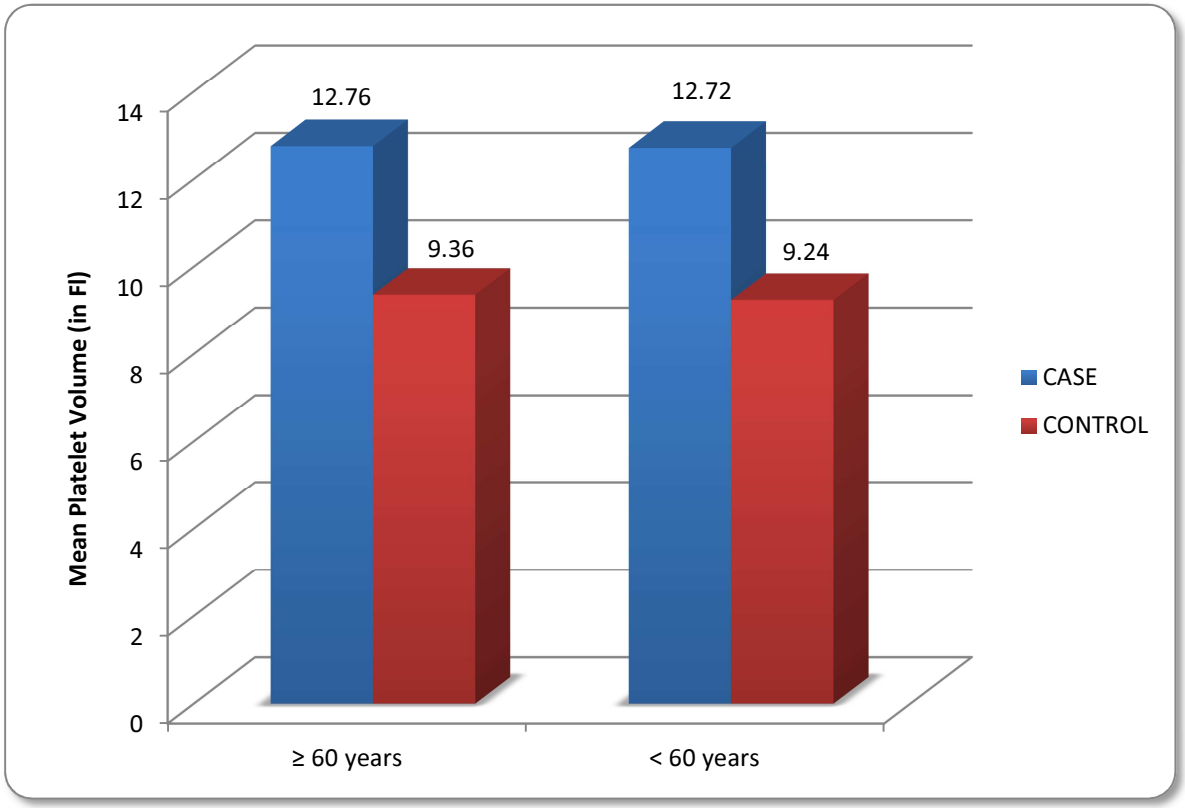


TABLE 11: MEAN PLATELET VOLUME AND HYPERTENSION

The mean platelet volume was higher among hypertensives, compared to non hypertensives and the difference was significant with a p value of 0.02. This implies that hypertension increases mean platelet volume thereby increasing the risk and severity of stroke.

RISK FACTOR	LEVELS	CASES	CONTROLS
HYPERTENSION	Hypertensives	12.59	9.33
	Non hypertensives	11.33	9.23
	P values	HT versus Non HT Cases – 0.02(significant) HT versus Non HT Controls – 0.06	

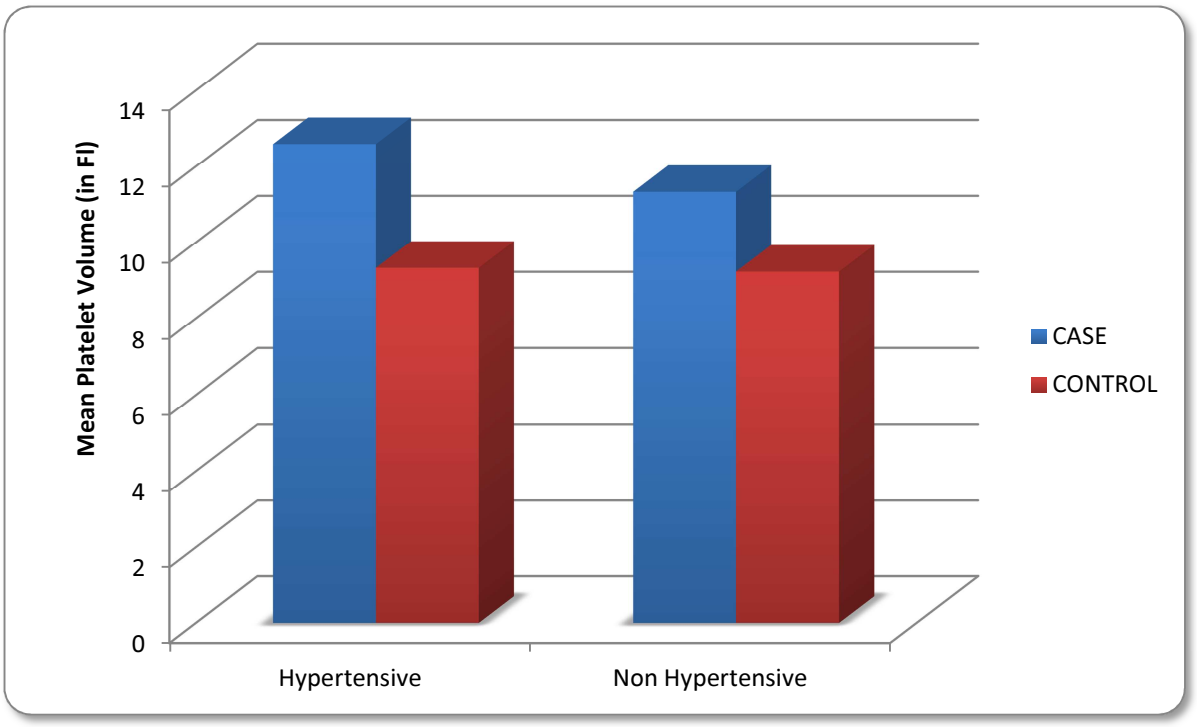


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TABLE 12: MEAN PLATELET VOLUME AND DIABETES MELLITUS

The mean platelet volume was slightly higher in both cases and controls with diabetes mellitus but the difference was not significant.

RISK FACTOR	LEVELS	CASES	CONTROLS
DIABETES MELLITUS	Diabetics	12.57	9.39
	Non diabetics	12.02	9.29
	P values	DM versus Non DM Cases – 0.28 DM versus Non DM Controls – 0.35	

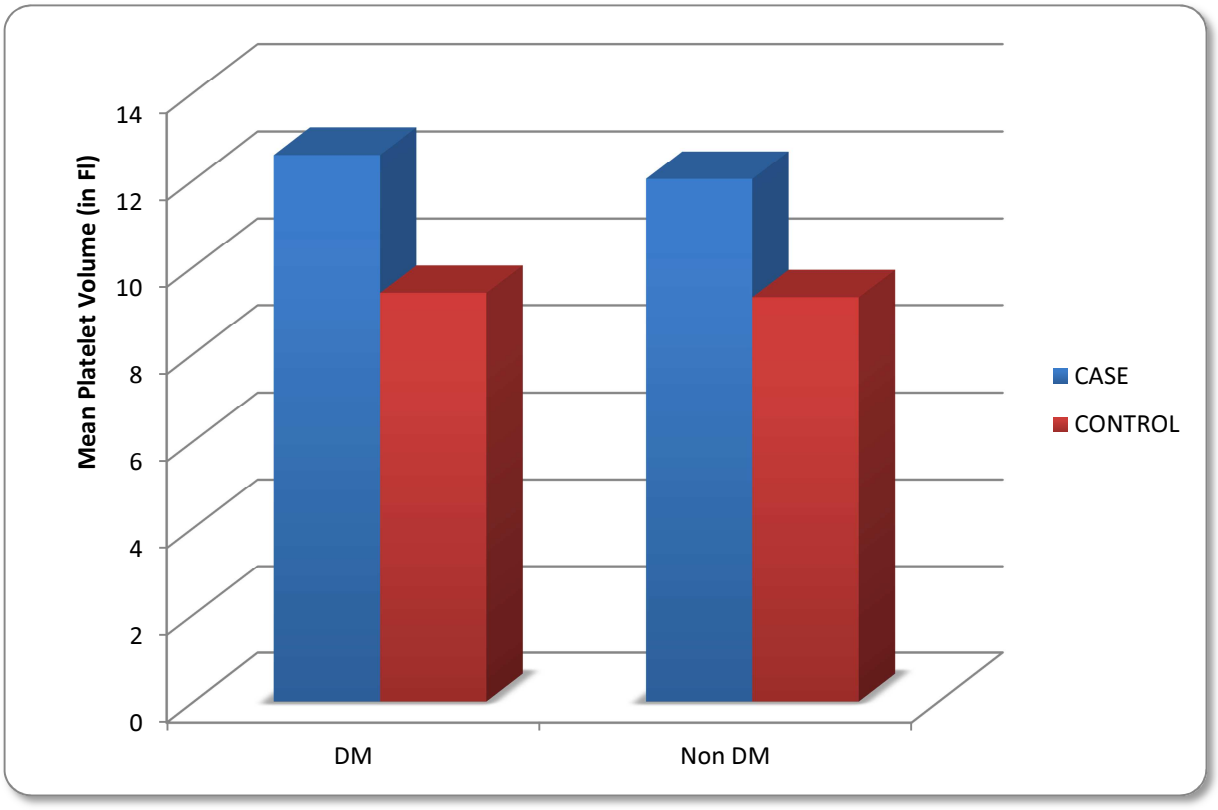


TABLE 13: MEAN PLATELET VOLUME AND DYSLIPIDEMIA

The mean platelet volume was slightly higher in patient with serum cholesterol greater than 200 compared to less than 200 but the difference was not statistically significant.

RISK FACTOR	LEVELS	CASES	CONTROLS
DYSLIPIDEMIA	Cholesterol>200	12.39	9.54
	Cholesterol<200	12.09	9.12
	P values	Cases – 0.55 Controls – 0.11	

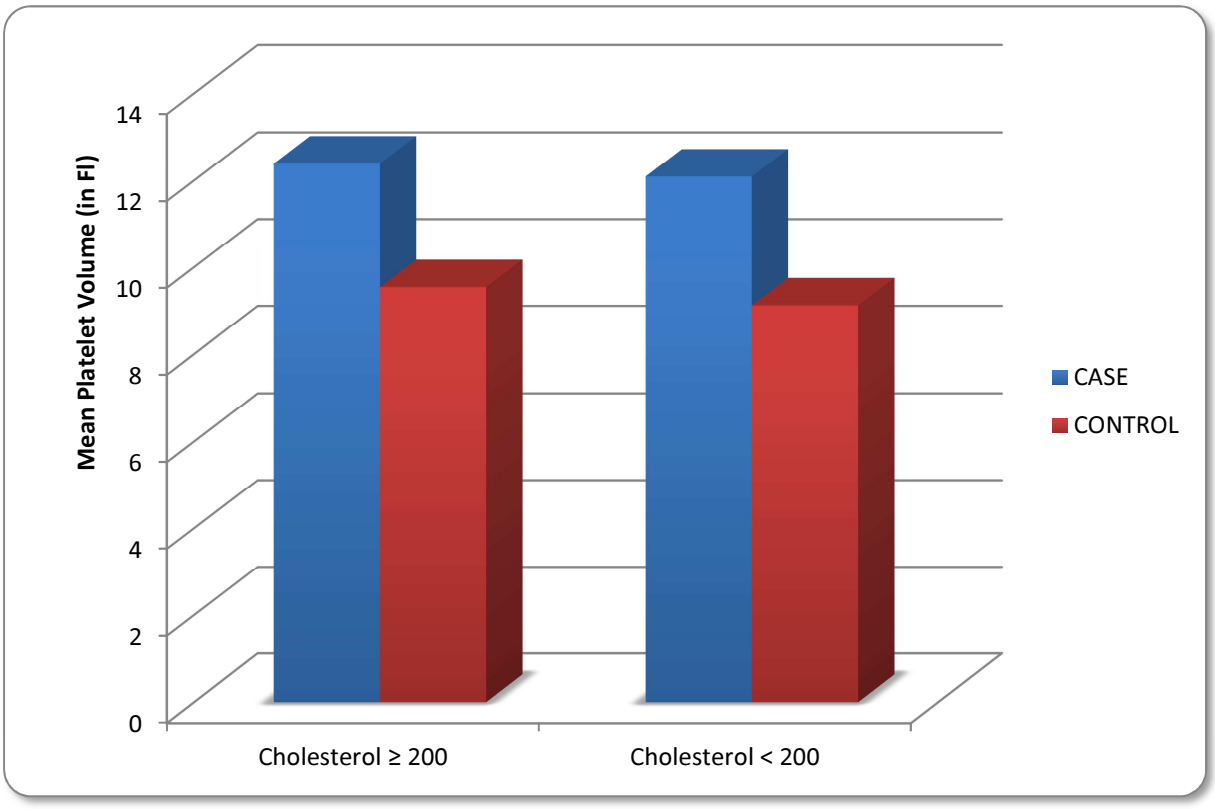


TABLE 14: MEAN PLATELET VOLUME AND SMOKING

The mean platelet volume is higher in smokers than in non smokers but the difference is not significant.

RISK FACTOR	LEVELS	CASES	CONTROLS
SMOKING	Smokers	12.48	9.34
	Non smokers	12.05	9.15
	P values	Smokers versus Non smokers Cases – 0.41 Smokers versus Non smokers Control- 0.32	

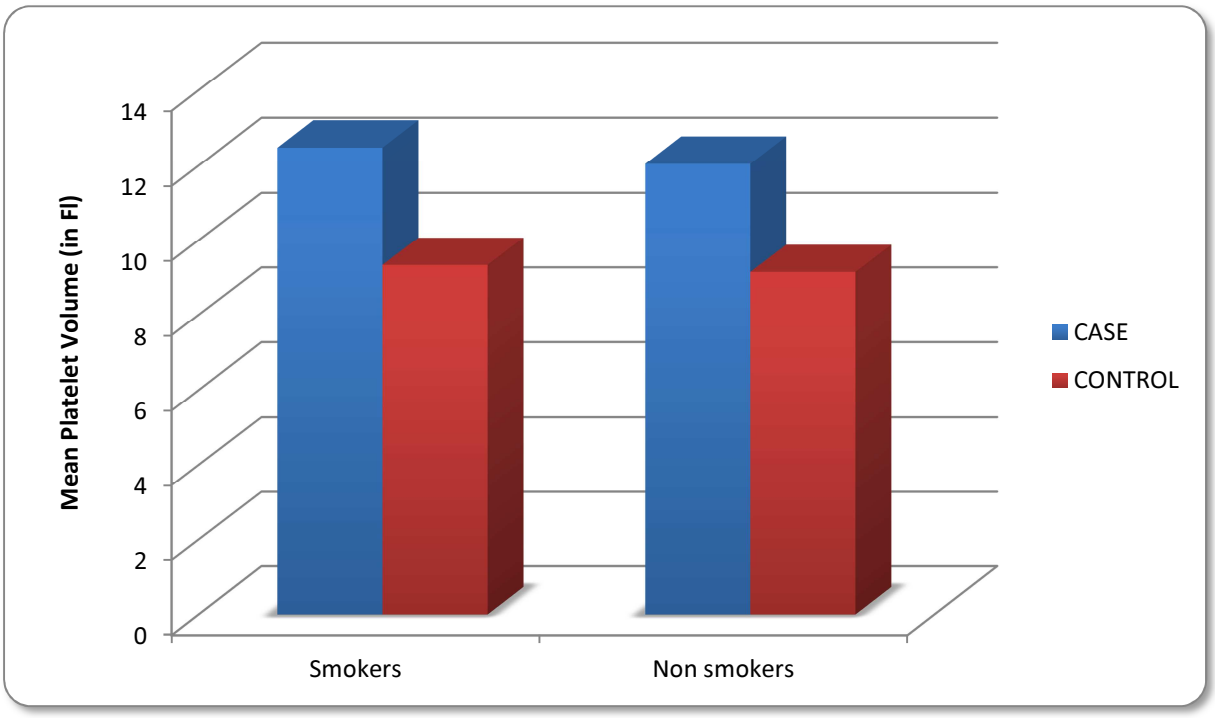


TABLE 15: MEAN PLATELET VOLUME AND ALCOHOL

Alcoholics had higher mean platelet volume compared to non alcoholics but the difference was not significant.

RISK FACTOR	LEVELS	CASES	CONTROLS
ALCOHOL	Alcoholics	12.30	9.42
	Non alcoholics	12.15	9.26
	P value	Alcoholic versus Non alcoholic cases- 0.77 Alcoholic versus Non alcoholic control- 0.45	

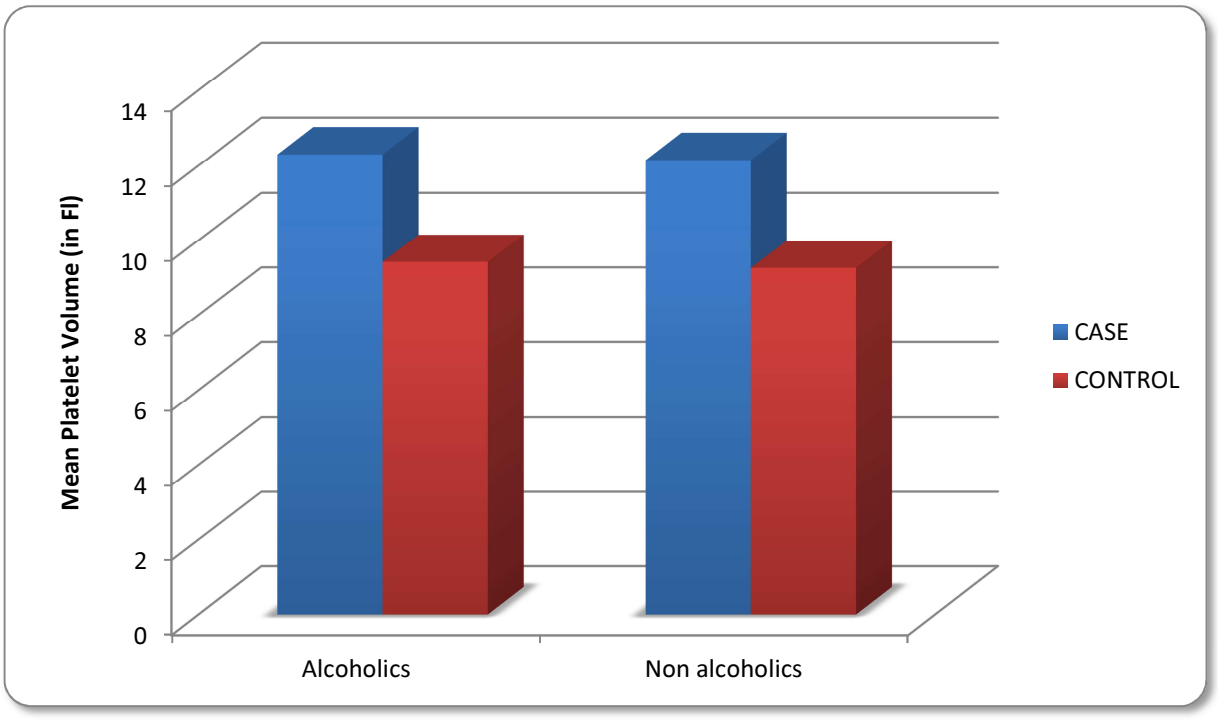


TABLE 16: CLINICAL SEVERITY OF STROKE AND MEAN PLATELET VOLUME

The clinical severity of stroke was assessed and graded according to Modified Rankin scale with scores varying from 0 having no significant disability to 6 implying death. The mean of mean platelet volumes of patients in each score from 0 to 6 was compared. The .patients who had a score of 6 i.e death had significantly elevated mean platelet volumes compared to lower scores like 0,1,2. There was no significant difference in other scores.

This implies that patients who have a higher mean platelet volume on day 1 have high risk of adverse outcomes including death compared to patients having low mean platelet volume.

MODIFIED RANKIN SCALE	PERCENTAGE OF PATIENTS	MEAN MPV
0	19	12.91
1	14	12.61
2	26	13.21
3	18	13.57
4	9	13.81
5	6	14.35
6	8	15.86

COMPARISON	P VALUE (unpaired t test)
MPV in patients with score 0 versus6 MPV in patients with score 1 versus 6 MPV in patients with score 2 versus 6	Less than 0.05 (significant)

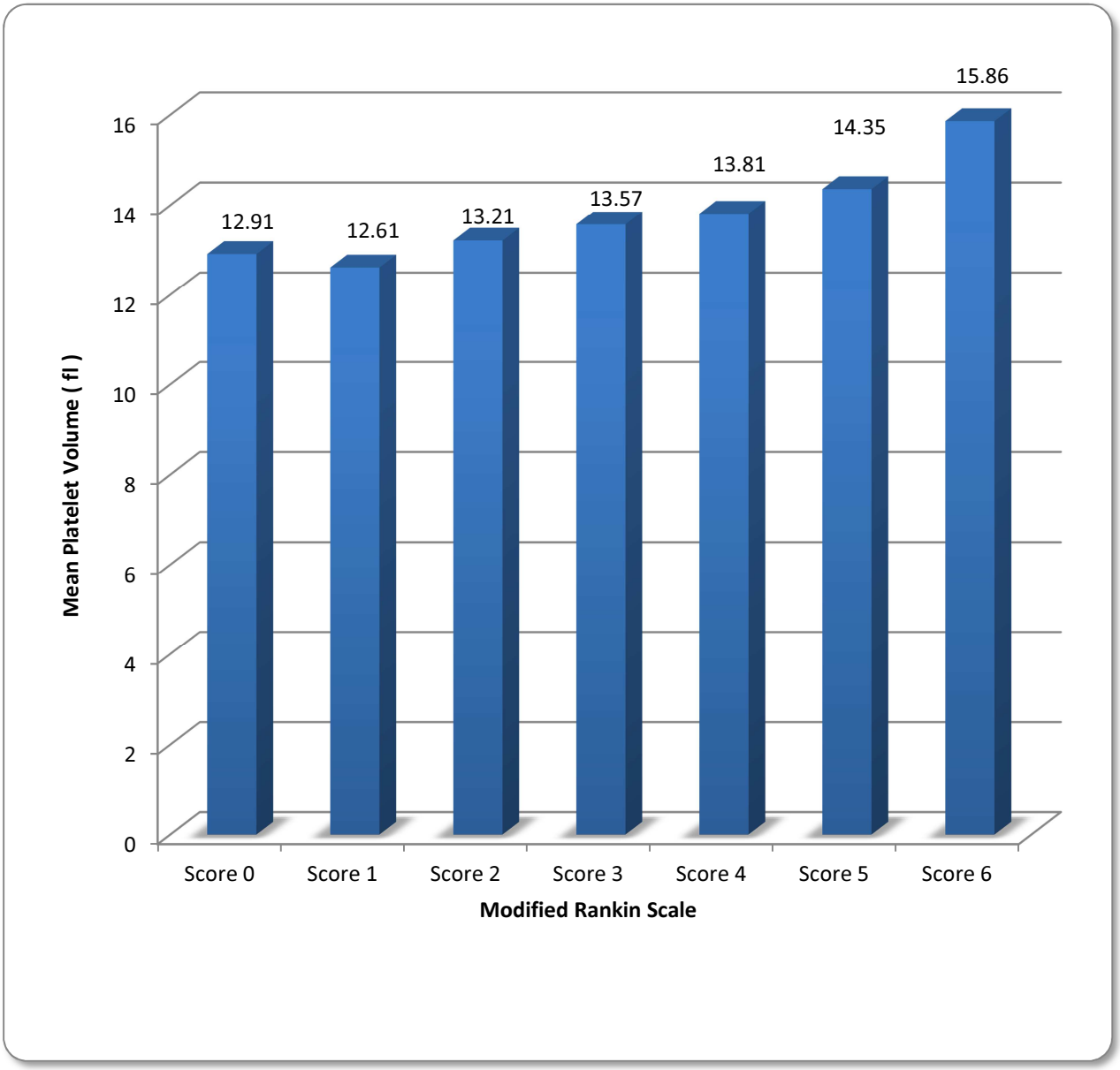
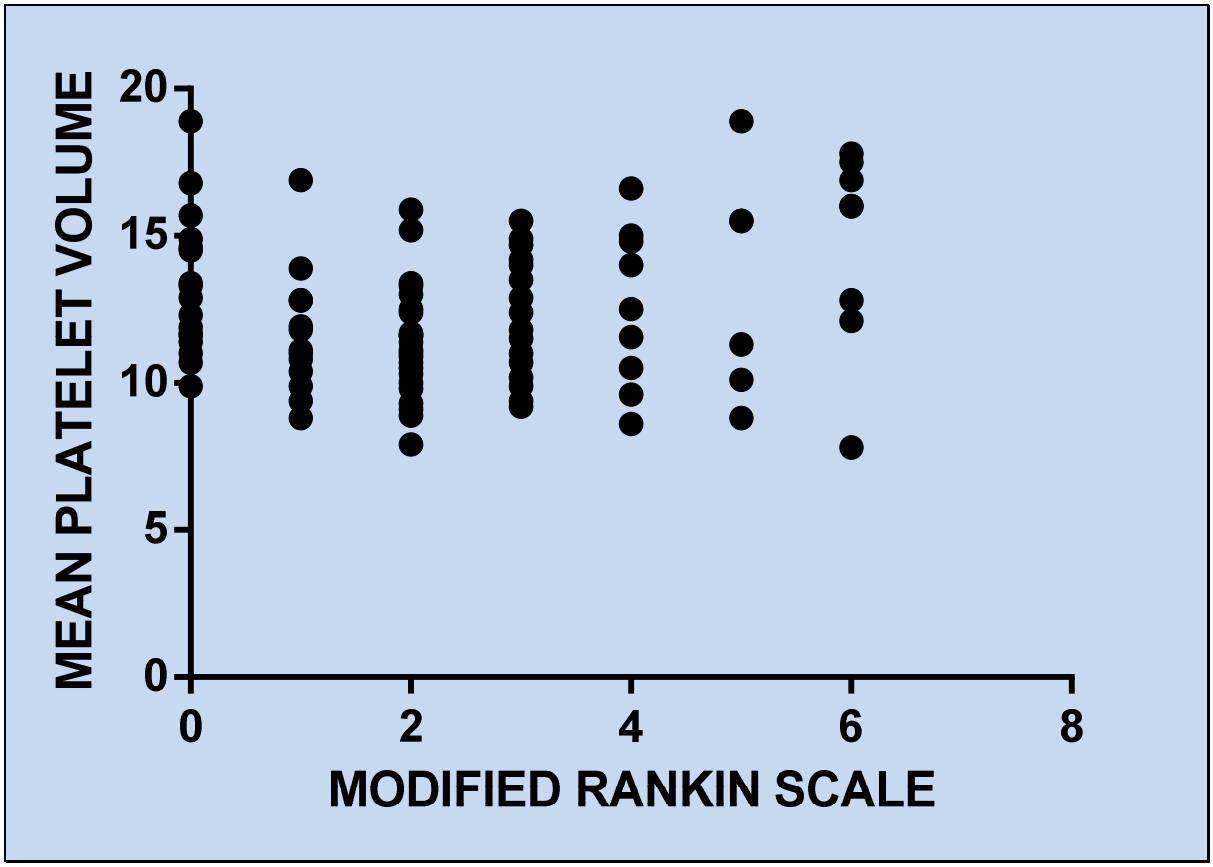


TABLE 17: MEAN PLATELET VOLUME AND MODIFIED RANKIN SCALE CORRELATION ANALYSIS

The correlation of mean platelet volume with the Modified Rankin Score was calculated using Pearson formula. Though a positive correlation was present, the correlation was not significant

MEAN PLATELET VOLUME AND MODIFIED RANKIN SCALE CORRELATION	PEARSON FORMULA	
	r value	0.1812
	Confidence interval	0.018 – 0.364
	P value	0.07 (Not significant)



DISCUSSION

This study is a case control study conducted on 100 patients with first episode of acute ischemic stroke and 50 controls. In 100 patients 60 were male and 40 were females. Out of 50 controls taken 30 were male, 20 female. The mean age of cases studied was 53.49 years when compared to 54.12 years for the controls. The maximum number of cases in this study were in the age group between 35-50 years. The mean age in males was 49.10 years, the mean age in female was 60.08 years.

The mean age group in our study was 53.49 years which was much lower compared to other studies. There was male preponderance in this study similar to all other studies except for O'Malley and Pikija et al that showed female preponderance.

RISK FACTORS FOR STROKE:

In this study hypertension was found to be most prevalent risk factor with 74% among cases and 60% among controls. Study conducted by A.Muscari et al showed hypertension is most prevalent risk factor with 84.7%[56]. Study conducted by Pikija et al showed hypertension is most common risk factor with 82.7%[57].

The next common risk factor is smoking, diabetes and then comes alcohol and dyslipidemia.

In this study men have higher incidence of ischemic stroke compared to women. Study conducted by Petty et al showed that age adjusted incidence of stroke rate is in more in men than in women[58]. Wiszniewska m et al conducted a study with risk factor distribution and concluded that female sex is associated with poor prognosis[59].

MPV AND RISK FACTORS:

In this study average mean platelet volume in hypertensive cases were 12.59 compared to 9.33 in controls. The mean platelet volume in non hypertensive cases was 11.33 compared to 9.33 in controls. The mean platelet volume elevation was statistically significant in hypertensives compared to non hypertensives with ischemic stroke with significant p value 0.02.This is similar to the study conducted by Coban E et al which showed significant elevation of MPV in hypertensives. The association of MPV with diabetes, smoking, alcohol were not statistically significant.

MPV AND GENDER:

Mean platelet volume in male cases was 12.27 and 12.25 in female cases. There were no significant differences between male and female. Many other studies also

did not show significant differences of mean platelet volume with gender except for the study done by Anna M.Butkiewicz et al which showed MPV was elevated in females.

MEAN PLATELET VOLUME AND ISCHEMIC STROKE

In this current study, MPV is significantly elevated in ischemic stroke patients compared to controls. This is similar to findings of Philips Bath et al in PROGRESS trial [63].

Elevation of MPV in the first day is associated with worst outcome. This was similar to the study conducted by Greisenegger et al which showed elevated MPV is associated with worst outcome.

In this study the MPV level remained to be constant for about a month, with factors like drugs not influencing it. This was similar to the study conducted by O'Malley et al who conducted study in 58 elderly stroke patients and measured platelet variables in acute (<48hours) and chronic(>6 months) of ischemic stroke. MPV was significantly elevated and platelet count was decreased in acute stroke compared with controls. There was no significant difference in MPV value after 6 months. [64]

In this study platelet count is showing slightly lower trend in the cases with an average of 1.84±0.27 when compared to controls 1.93±0.27.This is however not

statistically significant. This pattern has been seen in all other studies like O''Malley et al, Butter worth et al, Tohji et al.

MPV AND SEVERITY OF STROKE:

S. Greisenegger et al conducted a cross sectional study in 8 centers and applied modified Rankin scale after 1 week of acute ischemic stroke in 776 patients. It showed elevated MPV was associated with worst outcome[65]. In our study, though the correlation of MPV with severity of stroke using modified Rankin Scale did not show statistical significance, the MPV was significantly higher in patients with a score of 6 compared to lower scores like 0, 1 and 2 O'Malley conducted similar study with modified Rankin Scale and determined the outcome as independent (grade 0 to 2) dependent (grade 3 to 5) and dead (grade 6). In this study also no significant correlation between MPV and severity of ischemic stroke is found.

LIMITATIONS OF THE STUDY

1. The study sample size was small. There were only 100 patients and 50 controls in the study.

2. Seriously ill patients admitted in intensive care units were not included in this study due to difficulty in getting the consent. This might have lead to selection bias. This could have reflected on the correlation of MPV and the stroke severity.

3. The controls were matched only for age and sex and not for other risk factors which would have been ideal.

4. Long term follow up of the patients was difficult, so the follow up study was done for a short duration of 28 days. If the patients were followed up for 6 months as done in other studies, the correlation of MPV with modified Rankin Scale would be much more ideal.

CONCLUSION

The study had 100 patients and 50 age and sex matched controls. The main conclusions drawn from this study are

1. The mean platelet volume is significantly higher among stroke patients compared to controls.
2. The mean platelet volume tends to remain elevated at least for duration of 4 weeks after the onset of stroke.
3. The patients who had a higher mean platelet volume on day 1 compared to other patients had a high risk or adverse outcome including death.
4. Patients with hypertension had higher mean platelet volume compared to normotensives. Thus hypertensives had a higher risk of adverse outcomes.
5. Drugs like aspirin or statins did not alter the mean platelet volume over duration of 4 weeks.
6. There was no significant variation in mean platelet volumes with age, sex, diabetes, smoking and alcohol.

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ANNEXURE

"ASSESSMENT OF MEAN PLATELET VOLUME IN ISCHEMIC STROKE PATIENTS AND ITS CORRELATION WITH PROGNOSIS AND SEVERITY"

Name :

Age/Sex :

IP No :

Address :

Phone No. :

History	**Drug History**
❑ Smoking	❑ Anti platelet Drug
❑ Alcoholism	❑ Aspirin
❑ Diabetes	❑ Chemotherapy
❑ Systemic hypertension	❑ Other Drugs
❑ Coronary Artery Disease	
❑ Hyperlipidemia	

INVESTIGATIONS: **RFT**		
❑ Glucose		mg/dl
❑ Urea		mg/dl
❑ Creatinine		mg/dl
❑ Na+		mEq/l
❑ K+		mEq/l

	D1	D7	D28	
❑ WBC				$10^3/\mu L$
❑ RBC				$10^6/\mu L$
❑ Hemoglobin				gm/Dl
❑ HCT				%
❑ MCV				fL
❑ MCH				Pg
❑ MCHC				gm/dL
❑ Platelet Count				$10^3/\mu L$
❑ Lymphocyte %				%
❑ Mixed % (Basophilis, Eosinophils)				%
❑ Neutrophil %				%
❑ Lymphocyte #				$10^3/\mu L$
❑ Mixed #				$10^3/\mu L$
❑ Neutrophil #				$10^3/\mu L$
❑ Red cell distribution width				fL
❑ Platelet distribution width				fL
❑ Mean Platelet volume				fL
❑ P- LCR (large platelet ratio)				%
❑ CT Scan Brain				
❑ Area Involved				
❑ Carotid vertebral Dopler				
❑ Modified Rankin's Score				

INFORMATION SHEET

We are conducting a study on **"ASSESSMENT OF MEAN PLATELET VOLUME IN ISCHEMIC STROKE PATIENTS AND ITS CORRELATION WITH PROGNOSIS AND SEVERITY"** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to identify the association between mean platelet volume and ischemic stroke.

We are selecting certain cases and if you are found eligible, we may be using your blood samples to do special studies which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator Signature of Participant

Date :
Place :

PATIENT CONSENT FORM

Study Detail : "ASSESSMENT OF MEAN PLATELET VOLUME IN ISCHEMIC STROKE PATIENTS AND ITS CORRELATION WITH PROGNOSIS AND SEVERITY"

Study Centre : Rajiv Gandhi Government General Hospital, Chennai.

Patient's Name :

Patient's Age :

Identification Number :

Patient may check (√) these boxes

a) I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

b) I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

c) I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

d) I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

e) I hereby consent to participate in this study. ☐

f) I hereby give permission to undergo complete clinical examination and hematological tests. ☐

Signature of Investigator Signature/thumb impression

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. C. Poornima Raj
PG in MD General Medicine
Madras Medical College, Chennai -3

Dear Dr. C. Poornima Raj

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Assessment of mean platelet volume in ischemic stroke patients and its correlation with prognosis and severity" No.11062012,

The following members of Ethics Committee were present in the meeting held on 19.06.2012 conducted at Madras Medical College, Chennai -3.

1.	Dr. S.K. Rajan. M.D.,FRCP.,DSc	-- Chairperson
2.	Prof. K. Ramadevi MD Prof of Biochemistry, MMC, Ch-3	-- Member
3.	Prof. R. Nandhini MD Director, Inst. of Pharmacology ,MMC, Ch-3	-- Member
4.	Prof. C. Rajendiran, MD Director , Inst. of Internal Medicine, MMC, Ch-3	-- Member
5.	Prof. S. Deivanayagam MS Prof of Surgery, MMC, Ch-3	-- Member
6.	Prof. A. Radhakrishnan MD Prof of Internal Medicine, MMC, Ch-3	-- Member

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

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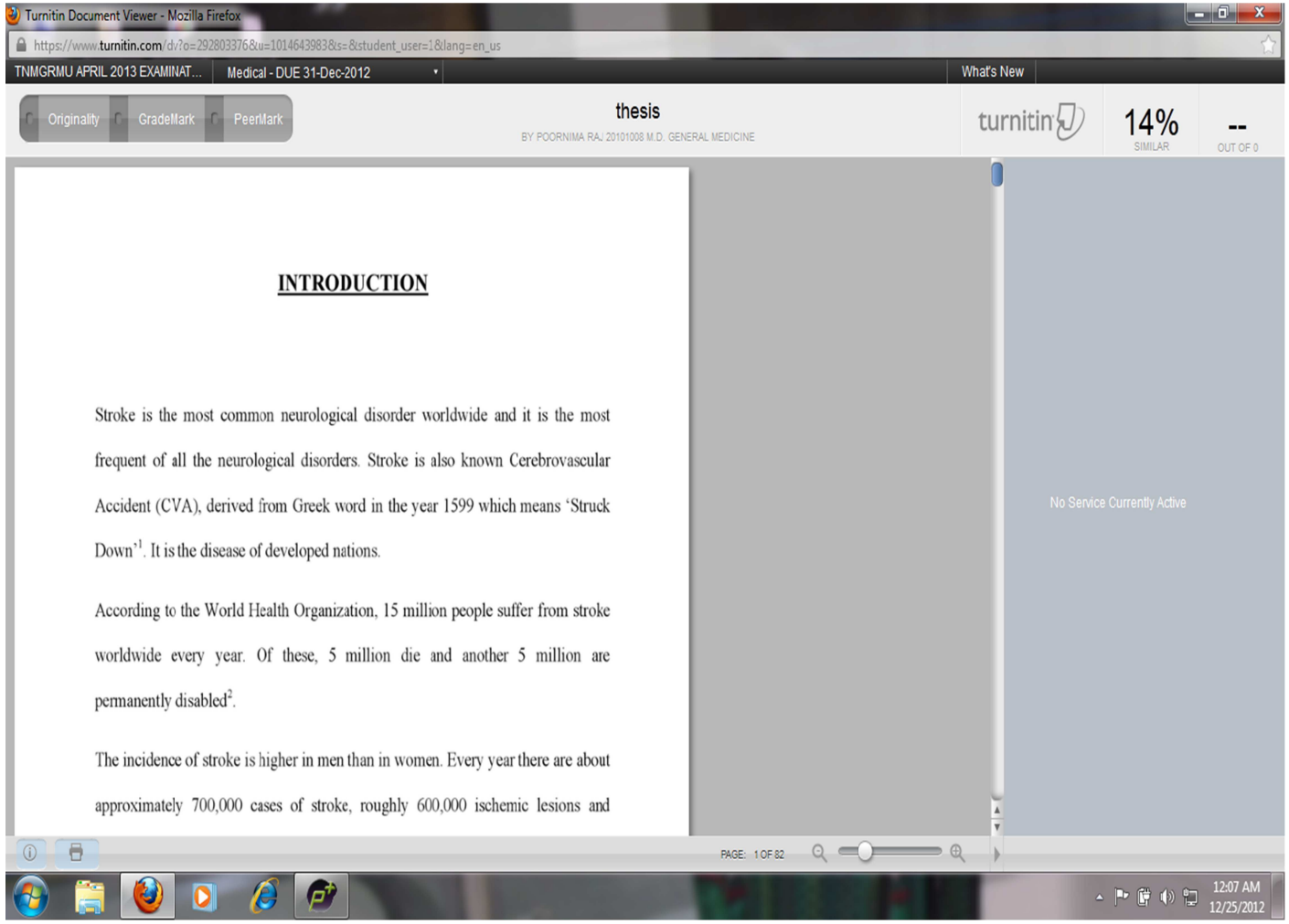
Introduction: Stroke is the most common neurological disorder world wide and its most frequent of all the neurological disorders.Stroke is also known CVA, derived from Greek word in 1599 which means 'Struck Down'. It is the disease of developed nations. According to the World Health Organization, 15 million people suffer stroke worldwide each year. Of these, 5 million die and another 5 million are permanently disabled. The stroke rate is higher in men than women. Every year there are about approximately 700,000 cases of stroke,roughly 600,000 ischemic lesions and 100,000 hemorrhages, with 175,000 fatalities from these causes. It is estimated that by 2020 stroke will become the 4 th leading...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INTRODUCTION
Stroke is the most common neurological disorder worldwide and it is the most frequent of all the neurological disorders. Stroke is also known Cerebrovascular Accident (CVA), derived from Greek word in the year 1599 which means 'Struck Down'[1]. It is the disease of developed nations.
According to the World Health Organization, 15 million people suffer from stroke worldwide every year. Of these, 5 million die and another 5 million are permanently disabled[2].
The incidence of stroke is higher in men than in women. Every year there are about approximately 700,000 cases of stroke, roughly 600,000 ischemic lesions and
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MASTER CHART

ID	Age	Sex	Smoking [Pack Years]	Alcoholism [n Years]	Hypertension [in years]	Diabetes	CAD	Total Cholestrol [in mg/dl]	Platelet count [in Lakhs]	MPV (fl)			Drugs	
										Day1	Day7	Day28	Asprin	Atorvas
1	38	M	0	0	N	N	N	135	1.64	8.9	8.9	8.9	N	N
2	71	F	0	0	Y	Y	Y	220	1.8	9.8	9.8	9.8	Y	Y
3	74	F	0	0	Y	Y	Y	225	1.5	10.1	10.1	10.1	Y	Y
4	38	M	0	0	N	N	N	150	1.95	9.1	9.1	9.1	N	N
5	58	M	20	15	Y	N	Y	114	1.55	10.3	10.3	10.3	Y	Y
6	75	M	0	0	Y	Y	Y	190	1.9	8.9	8.9	8.9	Y	Y
7	38	M	5	0	N	N	N	148	1.76	8.5	8.5	8.5	N	N
8	50	F	0	0	N	Y	N	132	1.63	10.2	10.2	10.2	N	N
9	60	F	0	0	Y	Y	Y	225	2.37	9.8	9.8	9.8	Y	Y
10	39	M	0	7	N	N	N	140	2.2	9.6	9.6	9.6	N	N
11	73	M	0	0	Y	Y	Y	176	2	9.1	9.1	9.1	Y	Y
12	45	M	13	11	Y	N	Y	290	2.25	9.8	9.8	9.8	Y	Y
13	67	M	25	25	Y	N	N	196	1.89	8.7	8.7	8.7	N	N
14	63	F	0	0	N	Y	Y	180	1.74	8.9	8.9	8.9	Y	Y
15	55	F	0	0	N	N	Y	193	1.78	9.2	9.2	9.2	Y	Y
16	68	F	0	0	Y	Y	Y	256	2.2	9.4	9.4	9.4	Y	Y
17	71	F	0	0	Y	Y	Y	229	1.97	9.1	9.1	9.1	Y	Y
18	46	M	0	6	Y	N	N	254	1.82	10.5	10.5	10.5	N	Y
19	65	F	0	0	Y	Y	Y	284	1.89	9.8	9.8	9.8	Y	Y
20	37	M	8	0	Y	N	N	200	2.25	9.8	9.8	9.8	N	N
21	70	F	0	0	Y	Y	Y	256	1.67	8.3	8.3	8.3	Y	Y
22	65	F	0	0	N	Y	Y	228	1.73	9.5	9.5	9.5	Y	Y
23	60	F	0	0	N	Y	Y	234	1.9	10.6	10.6	10.6	Y	Y
24	50	M	12	0	Y	N	N	180	1.6	8.1	8.1	8.1	N	N
25	44	F	0	0	N	N	N	175	1.93	9.1	9.1	9.1	N	N
26	61	F	0	0	Y	N	N	223	2.1	9.4	9.4	9.4	N	Y
27	42	F	0	0	N	N	N	143	1.73	9.5	9.5	9.5	N	N
28	38	M	5	0	Y	N	N	175	2.1	10.1	10.1	10.1	N	N
29	55	F	0	0	N	N	N	143	2.2	8.7	8.7	8.7	N	N
30	37	M	10	4	Y	N	N	140	2	8.5	8.6	8.5	N	N
31	51	F	0	0	N	N	N	133	1.9	8.9	8.9	8.9	N	N
32	39	M	0	0	N	N	N	195	2.45	8.6	8.6	8.6	N	N
33	41	M	6	7	Y	Y	N	220	1.45	9.7	9.7	9.7	N	Y
34	58	F	0	0	N	N	Y	241	2.11	9.6	9.6	9.6	Y	Y
35	63	F	0	0	Y	N	N	212	2.2	9.1	9.1	9.1	N	Y
36	64	M	20	0	N	Y	Y	242	2.1	9.3	9.3	9.3	Y	Y

37	45	F	0	0	N	Y	N	230	1.73	8.9	8.9	8.9	N	Y
38	36	M	0	2	N	N	N	177	2.23	9.2	9.2	9.2	N	N
39	74	M	40	38	Y	Y	Y	198	2.25	10	10	10	Y	Y
40	48	F	0	0	N	N	N	164	1.8	9.6	9.6	9.6	N	N
41	35	M	3	0	Y	N	N	135	2.2	8.3	8.3	8.3	N	N
42	40	M	5	4	Y	N	N	134	1.87	9.4	9.4	9.4	N	N
43	52	M	22	20	Y	Y	N	170	1.8	8.5	8.5	8.5	N	N
44	60	M	0	0	Y	N	Y	210	2.3	9.6	9.6	9.6	Y	Y
45	72	F	0	0	Y	Y	Y	210	2.16	9.4	9.4	9.4	Y	Y
46	52	F	0	0	Y	Y	N	156	1.55	9	9	9	N	N
47	56	F	0	0	Y	N	N	173	1.67	9.7	9.7	9.7	N	N
48	65	F	0	0	Y	N	N	170	2.65	9	9	9	N	N
49	61	F	0	0	Y	Y	Y	234	1.56	8.8	8.8	8.8	Y	Y
50	43	F	0	0	N	N	N	118	1.71	8.8	8.8	8.8	N	N